CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-476

Medical Review(s)

MEMORANDUM

DATE: December 6, 2004

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-476

SUBJECT: Recommendation for Approval Action for NDA 21-476, for the use of Lunesta (eszopiclone) in the treatment of patients with insomnia

NDA 21-476, for the use of Estorra (eszopiclone; new proposed tradename Lunesta) in the treatment of patients with insomnia, was submitted by Sepracor, Inc., on 1/30/03. Although the review team recommended that the sponsor be sent a Not Approvable letter on initial review (although efficacy had been demonstrated, there were concerns about safety based on evidence in animals that the drug was carcinogenic), Dr. Robert Temple, Director, Office of Drug Evaluation I, concluded that the application should be considered Approvable (see his memo of 3/4/04). For this reason, the Agency issued an Approvable letter on 2/27/04. In that letter, numerous requests were made:

1) additional analyses of human tumor data were requested
2) additional analyses of adverse events listed as "Infection" and "accidental injury" were requested
3) additional analyses of the effectiveness data were requested, based on our concerns that the high rate of "unpleasant taste" in the controlled trials could have invalidated the treatment blind
4) additional analyses of orthostatic vital sign and EKG data were requested
5) additional analyses of adverse events related to memory impairment and psychomotor impairment were requested
6) additional analyses of withdrawal phenomena and rebound insomnia were requested
7) the sponsor was requested to adopt specific dissolution specifications
8) the sponsor was asked to produce and make available a 1 mg tablet strength (a dose shown to be effective in elderly patients)
9) multiple CMC deficiencies were noted
10) the sponsor was requested to supply a new tradename, because their proposed name, ESTORRA, was found to bear an unacceptable similarity to the marketed drug ESTRACE.

The sponsor responded to the Approvable letter in a submission dated 6/14/04. The response has been reviewed by Dr. Karen Brugge, medical officer, Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics, Dr. Gurpreet Gill-Sangha, chemist, Dr. Aisar Atrakchi, pharmacologist, Dr. Michael

Klein, Controlled Substance Staff, Dr. James L. McVey, Microbiology, Dr. Jinhee L. Jahng, Division of Medication Errors and Technical Support, and Dr. Paul Andreason, Psychiatric Drugs Team Leader. The review team recommends that the application be approved.

I will very briefly review the sponsor's responses to the major questions posed in our Approvable letter, and offer the division's recommendations for action on the NDA.

Human Tumor Data

In the initial application, it was unclear how many human tumors were treatment emergent. In particular, a number of events appeared to have been neoplasia in a 6-month placebo controlled trial (Study 049). Given our primary concern about carcinogenicity, we had asked the sponsor for clarification and analyses of these data.

Upon re-analyses of these data, the sponsor noted 3 basal cell carcinomas (each of which were diagnosed about 150-170 days after treatment initiation, with some evidence that in two of these patients there was a lesion pre-existing prior to initiation of treatment) and 7 benign neoplastic events (2 uterine leimyomas, one each of cervical dysplasia, nevus, actinic keratosis, lipoma, and GI polyp) in the drug group and no tumors in the placebo group (see Tables 1-4 through 1-7 in Dr. Brugge's review, pages 14-17). There was a total of 427 patient-yrs of exposure to eszopiclone and 67 person-years of exposure to placebo (although Dr. Brugge concludes that exposure should not be expressed in person-yrs for data in a placebo controlled trial, I disagree; this is an entirely appropriate, and preferred way to compare exposures, especially in the context of controlled data).

There were two more malignancies (one basal cell, one ductal carcinoma in situ of the breast) in open label exposure, and 8 more benign neoplasms in open label exposure (3 of which were uterine leiomyomas). Dr. Brugge notes the occurrence of 9 cases of fibrocystic disease, although only 3 were in controlled trials (this represents 3/373 women treated with eszopiclone vs. 0/125 women receiving placebo).

Accidental Injury

The sponsor performed a detailed search of terms that could reasonably be considered to fall under the term "accidental injury". As Dr. Brugge notes, the largest difference in incidence was in the 6 month controlled trial, in which 10.1% of drug-treated patients experienced an injury, compared to 6.2% of placebo patients. There was no material difference in the rate of "falls" between these two groups in this study (0.8% vs 0.5%, drug and placebo rates, respectively). In the trials in elderly patients, 1.4% of eszopiclone-treated patients and 0.5% of

placebo-treated patients experienced "falls". There was no evidence that these events were related to hypotension.

Infection

The sponsor categorized infections into bacterial, viral, or fungal; Dr. Brugge describes the details of this categorization, but, in brief, this categorization was based on the verbatim term (e.g., "flu syndrome" as a verbatim term was considered a viral infection). In some cases, listed medication used to treat the infection was the basis for the categorization (e.g., if antibiotics were prescribed, the infection was considered bacterial).

In the 6-month study, 39% of eszopiclone and 28% of placebo treated patients had infections (in the 6 week study, 15% and 23% of placebo and eszopiclone patients, respectively, had infections). Table 2A-6 (Dr. Brugge's review, page 31) displays the incidence of viral infections in the 6 month study; as can be seen, only Pharyngitis and Infection were frequent and about twice the incidence in the drug compared to the placebo treated patients. In this 6 month study, the incidence of bacterial infection was 15% and 12% in the drug and placebo groups, respectively, with incidences of fungal infections of 3% and 1% in the drug and placebo groups, respectively. In the 6 week study, the incidence of viral infections was 19% and 13% in the drug and placebo groups, respectively. Incidences of bacterial and fungal infections were low (0-4% range, minimally greater on drug vs placebo).

Effectiveness

As noted above, we were concerned that the frequent occurrence of an unpleasant taste in the drug treated patients could have broken the blind. However, as Dr. Brugge describes, the sponsor has re-analyzed the data from multiple trials (transient insomnia, the 6 week trial, one of the two 2 week elderly trials, and the 6 month trial), in which they included only those patients who did not experience an unpleasant taste. The re-analyses revealed statistically significant drug-placebo differences.

Vital signs and EKG

There were no important differences between drug and placebo treated patients on the percentage of patients meeting outlier criteria for EKG intervals.

Regarding vital signs, the sponsor evaluated orthostatic vital signs in a single dose study in healthy volunteers, and in two seven day studies, one in elderly subjects, and one in younger adults.

In younger adults, episodes of orthostatic hypotension occurred in 2/12 subjects at Day 7 at 3 mg, and 0/12 at 6 mg. A total of 5/123 subject receiving a dose of 3

mg (combined Phase 1 studies of 1-7 days duration) had an episode of clinically significant decreased systolic blood pressure (< 90 mm Hg and > 20 mm Hg decrease from baseline) at 60 minutes post-dose; 2/52 subjects met this criterion at 60 minutes post-dose at 2 mg. Mean changes from baseline peaked at -5.3 mm Hg at 3 mg systolic and -2.8 mm Hg diastolic (with small increases in the placebo patients). There were no episodes of syncope in the database.

In elderly subjects in a 7 day study, small numbers of subjects experienced orthostatic hypotension between 30-90 minutes post-dose at doses of 3-5 mg, although the incidence was not consistently greater than in the placebo group (see, for example, Table 6A-3, Dr. Brugge's review, page 39-40). In this study, mean change in systolic blood pressure from baseline was maximal at -20 mm Hg at 3 mg (although placebo mean was -9 mm Hg) at 90 minutes post dose. The maximum recommended dose in the elderly is 2mg, a dose at which there were no important drug-placebo differences in vital signs.

In the 6 month controlled trial, eszopiclone treated patients had a 10% incidence of dizziness (no information related to blood pressure changes, if any, coincident with this adverse event) compared to 3% in the placebo group. In the elderly controlled studies, the rates were 6% and 2%, drug and placebo, respectively.

Cognitive and Psychomotor Effects

The sponsor evaluated cognitive, psychomotor, and memory function in two crossover studies evaluating 2 mg, 3 mg, and placebo, one in patients with chronic insomnia, one in healthy volunteers. The effects were measured 9.5 and 12.5 hours post-dose (next morning) with a battery of 20 tests. Rare individual tests showed some decrements on drug compared to placebo, with no discernible pattern of dose relatedness or consistent abnormality on any specific test (though of those tests that were abnormal, memory was the faculty most commonly affected).

In the 6 month controlled trial, 1.3% of drug treated and **XX** % of placebo treated patients reported memory impairment. In a 6 week non-elderly study, 3% of patients treated with 3 mg reported confusion, compared to 0% for the 2 mg and placebo groups. In one 2 week study in elderly patients, 2.5 % of patients treated with 2 mg reported confusion, compared to 0% in the 1 mg and placebo groups (in a second similar study, there were no reports of confusion).

Withdrawal effects (Anxiety and Rebound Insomnia)

Low rates of anxiety were reported in the controlled trials (see draft labeling for a description).

Rebound insomnia (defined as a worsening of insomnia compared to baseline

after treatment discontinuation) was evaluated in a 6 week study (2 mg, 3 mg, placebo) on the first 2 days after treatment discontinuation.

Significant rebound was noted on the first post-treatment day on sleep latency and wakenings after sleep onset in the patients previously treated with 2 mg. These parameters resolved by the second post-treatment night, and no significant rebound on these measures occurred in the (previously treated) 3 mg group, although in this dose group, sleep efficiency was reduced on the first post-dosing night.

Dissolution Specifications

The sponsor has adopted the Agency's proposed dissolution specifications.

One mg tablet

As noted, the Agency requested that the sponsor produce a 1 mg tablet, because this dose was effective in elderly patients. The sponsor has done this, and the chemist and the OCPB reviewer consider the relevant data for this tablet acceptable.

CMC

The CMC deficiencies described in the Approvable letter have been resolved.

New Name

The sponsor has proposed a new tradename, Lunesta, that has been found acceptable by both DMETS and DDMAC.

Labeling

We have attached a version of draft labeling which has been discussed with the sponsor, and on which we have agreed. The major sections that are new (in comparison to the draft sent with the Approvable letter) are a section in the Clinical Trials section related to safety concerns for sedative/hypnotic drugs and the Adverse Events Tables. The former is a standard sub-section in labeling for these drugs, but the sponsor had not included such a section in their originally proposed labeling; we had asked them to do so in the Approvable label. This sub-section now consists of two parts: a Cognitive, Memory, Sedative, and Psychomotor Effects section, and a Withdrawal Emergent Anxiety and Insomnia section.

Regarding the Adverse Event Tables, in our Approvable letter, we had asked for three tables: one which compared ADR incidences on drug to placebo in all controlled trials, one which included ADR incidences in all controlled trials but

broken down by age (elderly data separately from young adult data), and one in which those ADRs that were dose related (both ages combined) were presented.

The firm has submitted two tables (each containing the data from the most relevant controlled trials in each age group), and added text to describe those that are dose related in each case (there are few of these). We have found this acceptable.

COMMENTS

The sponsor has responded adequately to all of the questions posed in our Approvable letter. Not unexpectedly, the data do not suggest a signal for the occurrence of malignancies (at least not in the controlled trials). None of the other re-analyses of the safety issues raised in the Approvable letter have identified issues that would preclude Approval of the application at this time, and we believe the attached draft labeling accurately describes the data.

For these reasons, then, we recommend that the application be approved, and that the attached Approval letter with appended labeling be issued.

Russell Katz, M.D.

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/s/

Russell Katz
12/15/04 12:51:56 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	21-476
Sponsor:	Sepracor Inc
Drug	
Established Name:	Eszoplicone
Chemical Name:	(+)-(5S)-6-(chloropyridine-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate
Code Name:	NA
Formulation:	2 and 3 mg oral tablets
Indication:	Chronic and Transient Insomnia
Dates of Submission:	Letter Date: 6/14/04 Submission EDR Date: 6/17/04
Materials Reviewed:	Response to February 25, 2004 Approvable Letter
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	10/18/04

I. Background.

The purpose of the submission is to assist the Team Leader and Division Director of the Division of Neuropharmacological Drug Products in the regulatory processing of this NDA.

The current submission is a response to a 2/25/04 Approvable Letter. This reviewer, recommended in the Clinical review of the original NDA submission, that the NDA not be given an approvable status. However, the submission was given an approvable action at the Agency Level. Therefore this review focuses on individual clinical items raised in the 2/25/04 Approvable Letter provides reviewer comments and recommendations to each of these items.

The Structure of this Review. The sponsor itemized each bulleted item in the Approvable Letter, as well as some bracketed comments in labeling that was attached to the Approvable letter and categorized each comment as follows:

- "Clinical" Comments: 1,2 A and B, 3, 6A-C (these items were responses to specific safety or related information), 10-14 (these items related to the Safety Update information), 15 (on postmarketing experience), 16 (English translations to foreign approved labeling)
- "Clinical Labeling" Comments: 7 A and B, 8, 9 A-G (these items are additional safety related items). These items appeared either as comments in the Approvable

letter (Items 7-8) or as bracketed comments in labeling attached to the Approvable Letter (Items 9, A-G).

- Additional Comments of the Approvable Letter that are itemized by the sponsor as follows: Comments 4 (Controlled Substance Staff related topic), 5 (CMC topic), 17 (OCPB item), 18 (CMC item), 19 (on nomenclature for the drug, a DMET item)
- Comment 20 regarding the Pediatric Research Equity Act (PREA)
- Comment 21 (Promotional Materials and Advertising information).

This review has the sections that provide the sponsor's response, reviewer comments, conclusions and recommendations (including pertinent labeling recommendations) regarding each of the above itemized comments in the Approvable letter, as itemized by the sponsor in their response submission. The sections were organized with the effort to group itemized comments that are related as described in the following:

- **Section II** on Specific Safety Concerns in the Approvable Letter: Comments 1, 2 A and B, 3, 6A-C, 10-16 that are regarding specific safety concerns (corresponding to bulleted comments in the Approvable letter, as previous described).
- **Section III** on Drug Class Safety Concerns (comments in the Approvable Letter or in bracketed comments in attached labeling) and Other Bracketed Labeling Comments in Labeling (attached to the Approvable Letter to which the sponsor responded as itemized comments in the response submission):
  - Clinical comments (7 and 8) related to safety issues (such as memory, cognitive and psychomotor function effects) for the drug class including bracketed labeling comment itemized by the sponsor as 9 A (attached to the Approved Letter) regarding the section on "Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs."
  - Other bracketed comments in labeling attached to the Approvable letter (portions of Comment 9A and 9B-G).
- **Section IV on Updated Safety-Related Information:** Comments 10-16 (in the Approvable Letter) that pertain to updated safety-related information.
- **Section V on Comments Related to Other Specialties:** Additional Comments: Items 4-5, 17, 18, and 19 that focus on CMC, OCPB or DMET topics
- **Section VI Pediatric Research:** Comment 20 on PREA.
- **Section VII. Promotional Materials:** Comment 21 on Promotional/Advertising information.
- **Section VIII. Overall Conclusions and Additional Key Labeling Recommendations, Not Addressed in Previous Sections:** this section addresses issues not addressed elsewhere in the review.

The above itemized comments are henceforth referred to as items in this review (rather than as comments).

The sponsor's response (not italicized), and reviewer's comments and recommendations (italicized subsections) are provided for each item of each section.

The final section of this review (Section VI) addresses additional key labeling issues.

II. Clinical Items in the Approvable Letter

The Sponsor's Response to Each Clinical Item in the 2/25/04 Approvable Letter
Each Item below corresponds to each item in the response submission. See the above section for details on the structure of this review. Each Item is followed by a copy of the comments of the Approvable Letter to which the given item refers. Non-itealicezed sections describe the sponsor's response. Italicized sections reflect reviewer comments, conclusions and/or recommendations the given item.

Clinical Item 1. Adverse Events of Neoplasia

Item 1 in the Approvable Letter.

Please clarify the actual numbers of reports of neoplasm in study 190-049. There appears to be a disproportionate number of reports of adverse events of neoplasia in the eszopiclone group in this long-term double blind study of eszopiclone in patients with chronic insomnia. Depending on the tables we consult there are somewhere between 16 and 24 reports of neoplasia in the 593 eszopiclone treated patients and 0/195 reports in the placebo group. We recognize from the verbatim terms that many of these reports may have been improperly coded; however, in the absence of the patient data or a clearer explanation, we cannot make that assumption. Though we are interested in an explanation of all of these cases, we are particularly curious about three cases:

a. Subject 0450024- by your description, this patient seems to be progressing steadily in a work up for disseminated cancer and then appears lost to follow-up after she drops out of the study. This case was not reported as a serious adverse event even though the reason for her discontinuation is coded as "neoplasia".

Continued on the next page...

b. Subject 0406001- dropped out of the study for an adverse event coded as Breast Neoplasm. The summary reports that she experienced a "lump" in her left breast after approximately 1½ months of double-blind treatment. It was considered benign, presumably based on ultrasound and mammography that were conducted, but the results were not described. The subsequent course of her breast lump over time was not described yet study drug was discontinued upon discovery of the lump.

c. Subject 0421004- a 62 year old female with no medical problems at screening who reported a "nodule in throat" after approximately 5 months of double-blind treatment. This nodule was described as resolving 10 days after cessation of treatment. The narrative provides no other information and she appears lost to follow-up.

Once all of the cases have been adequately examined, comparative incidence rates for the occurrence of neoplasia need to be calculated. Of the potential comparisons that you may make on the occurrence rates for neoplasia, one should be based on patient-years exposure to drug or placebo. If patients were lost to follow-up before a definitive diagnosis of the problem was made, then these cases should be counted as neoplasia in at least one analysis. It will also be important to examine the timing of the observations of neoplasia, as the plausibility of such an event as drug-related could be affected (e.g., a finding at 2-4 weeks would not be plausibly drug-related but one at 6 months might be).

We can not say that these cases represent a persuasive signal of drug-induced neoplasia, but the numerical imbalance of the reports of neoplasia and case histories that these numbers represent need to be thoroughly examined prior to considering eszopiclone for approval, especially given the pre-clinical findings of mammary and lung tumors with zopiclone and the finding of clastogenicity of eszopiclone and S-desmethyl-zopiclone.

Sponsor's Response to Item 1.

A. Narrative Descriptions of 3 Subjects of Interest (Subjects 0450024, 0406001, and 0421004) Requested in the Approvable Letter under Item 1 and Reviewer Comments. Subjects 0406001 and 0421008 *are described in subsections below on "Breast Events ..." and on "Other Neoplasias...," respectively. Upon a review of the narratives of these subjects, the former subject most likely had fibrocystic disease (examined by mammography). The latter subject most likely had throat or esophageal related complication (complained of a "knot or lump" in the throat that worsened with swallowing, diagnosed as "globus") due to gastro-esophageal reflux (the symptoms were accompanied by this condition and were reported approximately 2 ½ weeks after starting lipitor).*

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The third subject (subject 0450024) had multiple tumors revealed by CT scan or other imaging techniques (bilateral breasts, liver, pulmonary and a renal cyst). The etiology of these tumors and ascertaining a potential role of the study drug is more complicated.

The breast and renal tumors were reported as cystic and breast findings were found at baseline and were bilateral. These observations suggest non-neoplastic and non-drug-related pre-existing conditions. Yet, the status of the breast findings during treatment in the study is not adequately documented to determine if a potential contributory role of the study existed in the progression of the breast-related pre-existing condition. A potential role of the study drug is a potentially serious concern, given other clinical observations for a greater incidence of potentially related events in longer term trials (breast pain, engorgement and dysmennorhea, among others) and given the preclinical mammary gland tumor findings (refer to the Pharmacology Toxicology review of the original NDA). Yet, the breast condition is likely to be fibrocystic disease on the basis of the information provided. However a definitive diagnoses remains unclear.

The pulmonary and liver tumors found on CT scan of the above subject (subject 0450024) may be neoplasia and the role of the study drug in at least as a contributory factor to these conditions remains unclear. Yet, the subject is reportedly stable based on self-report to the sponsor when they contacted the subject in March of 2004 (the subject withdrew from the study approximately 2 and half years ago). However, a completed diagnostic work-up for any of the tumors cannot be found in the narratives (e.g. hepatitis screen, biopsy, among others). In conclusion, information remains inadequate to verify that this subject does not have neoplasia and that the study drug did not play a role in events during the study. See below for a more detailed description of this subject.

A More Detailed Description of Subject 0450024 with Multiple Nodules with Multi-organ Involvement (renal, breast, lung and liver). *The third subject of interest has a complicated history and presentation. Furthermore, the etiology and/or diagnosis of the nodules remain unclear. Therefore, this subject is described in more detail in the following (refer to the above synopsis for a brief summary of this subject). Refer to the review of the original NDA for background information on this subject. The following summarizes any new and/or relevant information found in an updated narrative provided in the current submission.*

The subject had abdominal and CT scans on Day 176 of ESZ treatment for evaluation of abdominal pain by her gynecologist (the narrative in the original NDA indicated the subject was 43 year old, although other information appears similar to information provided in the current submission, but in less detail and without more recently obtained information). These findings resulted in early withdrawal from the study on November 9, 2001.

Upon review of the narrative that included some updated information (upon contacting the subject on 3/15/2004) this subject was found to be stable since almost 3 years ago when the multi-organ "nodules" were first revealed by CT. The subject underwent spine surgery in 2002 and follow-up chest CT scans revealed a "stable pulmonary nodule," except a "slight interval increase in size" that "may be due to slight difference in patient positioning" (the sponsor provided these phrases, as quotes) on 1/16/02. A subsequent chest CT on [redacted] there was "no change in the sized" of the nodule. No adenopathy was found on CT and no other nodules or masses are described. The subject is a 28 year 1 ½ packs/day smoker who stopped in 2000. The etiology of the pulmonary nodule remains unclear to this reviewer.

Regarding the liver hypo-dense nodules found in the initial abdominal CT in subject 0450024, the sponsor only indicates that this subject had elevated ALT at screening and study Visit 5 (42 and 51 U/l, respectively) with no history of alcohol or drug abuse. No other information is provided regarding the liver lesions and regarding the renal cyst (also found on the initial abdominal CT). No comment on the status of these lesions over time or comment about any follow-up diagnostic tests could be found in the narrative. A general comment was provided, based on the subject's self report (upon a recent contact with the subject), that the subject was stable, asymptomatic, well, and not aware of requiring any further follow-up evaluations (last radiographic follow-up was in 2002, 2 years before the subject was last contacted). This reviewer is unclear as to the etiology of any of the nodules found in this subject.

Subject 0450024 also had "small fairly well defined nodular densities in both breasts" and a normal chest x-ray at screening. At baseline the diagnosis was (as quoted by the sponsor): "Bi-Rads Category 2-Benign Finding: Benign nodular densities in both breast." A follow-up ultrasound revealed no identifiable mass. This subject is likely to have fibrocystic breast disease at baseline. The outcome of this condition during and after the study is not described in the narrative, other than the general statement thatthe subject was stable, as previously described.

In conclusion, Subject 0450024 remains stable regarding the pulmonary nodule. It is not clear if the liver nodules are neoplastic or neoplastic metastesic tumors from the pulmonary nodule. Yet as above, this subject has been "stable." The definitive diagnoses of the nodules in any of the subject's organs remains unclear. However, the renal and breast lesions are reportedly cystic in nature and are likely to be benign non-neoplastic events. Yet, the outcome of either of these lesions and their diagnosis upon follow-up remains unclear. Despite these caveats the patient who was recently contacted, reported being well and asymptomatic and she was unaware of plans for additional scans (it is not clear if this part of the narrative is only referring to chest scans and the pulmonary nodule). Typically if the subject had a malignancy such as in the lung and liver and possibly in the breast, she would be having signs and symptoms and metastases after four years from the time the nodules were first found. However, consideration must be given to the possibility that she may have neoplasia that may be malignant (e.g. pulmonary).

B. A Search and Review of Adverse Events reported as Neoplasia in the Chronic Insomnia Trial (Study 190-049)

The sponsor provided a listing of adverse events (AEs) found in the database search of AEs reported as neoplasia or related events in the longterm Chronic Insomnia trial, Study 190-049. The sponsor had these events classified on the basis of the likelihood that a given event was malignant, benign or non-neoplastic in nature. The methods for this search and for classifying the events is described later.

Before showing the sponsor's results of their classification system, a synopsis is first provided and recommendations. The synopsis summarizes neoplasias enumerated by this reviewer on the basis of a review of narratives of the AEs provided by the sponsor (the sponsor provided narratives for AEs captured by their search of AEs of neoplasias in the

long term Chronic Insomnia Trial, Study 190-049). Refer to the review of the original NDA for additional background information.

After the synopsis and reviewer recommendations (italicized subsections), the following subsections provide more detailed information:

- A subsection of the sponsor's enumeration of neoplasia events based on their classification method is provided (non-italicized subsection),
- Followed by a more detailed description of the reviewer's methods for classifying AEs of neoplasia and reviewer observations based on a review of the narrative information. These subsections include a description of gynecological events.

All sections reflecting reviewer's comments and observations are italicized.

Reviewer Synopsis of Sponsor's Response to Item 1: Exposure, Adverse Events of Neoplasia, and Reviewer Conclusions

Summary of Background and of Reviewer's Findings Upon Review of Narratives Provided in the Current Submission. *Refer to the original review of the NDA regarding concerns for a signal for adverse events of "neoplasia" in the longterm trial, Study 190-049. The Approvable Letter requested more detailed information and clarification of the adverse events reported as "neoplasia" and other events that may be neoplastic in nature in this Chronic Insomnia Phase III trial (refer to the above copy of the relevant section of the Approvable Letter). The sponsor was also asked in the Approvable letter to determine the incidence of events of neoplasia in this trial.*

Study 190-049 was a longterm Chronic Insomnia Phase III trial. This trial included almost exclusively non-elderly adults that received 6-months of double-blind placebo or ESZ (3 mg daily; 593 eszopiclone and 195 placebo ITT safety subjects) followed by open label ESZ (3 mg daily) for 6-months (471 ITT safety subjects).

A review of information in the current submission yielded multiple events of neoplasia involving skin and other organ systems (e.g. breast) in subjects of the longterm Chronic Insomnia trial, Study 190-049. Given the complexity in classifying these subjects, limitations with the information on these adverse events reported as events of neoplasia, fairly stringent eligibility criteria with respect to ruling out pre-existing neoplasia, as well as other potential problems with interpreting the findings, a consult was requested from the Division of Oncology Drug Products.

Since a signal for gynecological events appears to exist and the potential for a gynecological neoplasia signal is an additional concern, a consult was requested from the Division of Reproductive Urological Drug Products (preclinical findings of mammary gland tumors, as described in the Pharmacology Toxicology review of the original NDA and clinical gynecological events in longterm trials described in this review and in the clinical review of the original NDA).

Consultative input is pending at the time of this writing.

In response to the approvable letter regarding events of neoplasia in Study 190-049, the sponsor conducted a search for any adverse event reported as a neoplasia in Study 190-049, as described later. Using methods described later in this review, the sponsor had the events categorized into events of malignant neoplasia, benign neoplasia, probable or possible events of neoplasia, and other categories). The sponsor provided summary tables listing events within each category, which will be provided later in this review. Narratives for all events listed in these tables (all event obtained from their database search) were also provided in the submission.

Instead of relying on the sponsor's summary tables and methods of classifying he neoplasia events, this reviewer opted to use a conservative approach in identifying events of neoplasia and events of probable or possible neoplasia. Each narrative was therefore reviewed and on the basis of information in the narratives, a review strategy was employed for classifying these events as neoplasia events, as described later.

A Summary of Drug Exposure in the Longterm Trial. *Since the interpretation of events of neoplasia, in part, hinges on the extent of drug exposure in Study 190-049 this section focuses on a description of drug exposure. This reviewer used a conservative approach in describing exposure (patient years were not used for reasons provided later).*

The ITT Safety population consisted of the following in each phase of the study (enumeration of female subjects is also provided since common events included female gynecological events and the numbers were taken from summary tables on demographic features of the study population, refer to the original NDA review):

- *DB Phase:*
  - *593 ESZ subjects and 195 Placebo subjects*
  - *Females: 373 ESZ subjects and 125 Placebo subjects*
- *OL Phase:*
  - *471 OL ESZ subjects of which 360 subjects previously received DB ESZ*
  - *Female subjects: 295 OL ESZ subjects, the number previously treated with DB ESZ could not be found*

The number of completers in Study 190-049:

- *DB Phase:*
  - *360 ESZ subjects and 111 placebo subjects*
  - *Females: could not find this number*
- *OL Phase:*
  - *382 subjects of which 296 subjects were previously exposed to DB ESZ*
  - *Females: the number cannot be found*

Summary of the Enumeration of Subjects with Events of Neoplasia Based on a Review of Narratives *The following paragraphs summarize the enumeration of cases of neoplasia or related events on the basis of a review of the narratives, using a review strategy for identifying events of concern, as described in more detail later in this review.*

More detailed descriptions of the events of concern, the rationale for conclusions about the cause/diagnosis of the event and other comments are provided in later subsections. .

Clear or Probable Malignancies were found for the skin (at least 5 ESZ subjects and no placebo) and breast (1 clear diagnosis in ESZ subjects and no placebo subjects):

- ***3 Skin malignancies in the DB phase:*** *3 (subjects are listed in the sponsor's summary Table 1-2 of malignant events, of which a copy is provided in this review) out of 593 ITT safety subjects in the DB phase (basal cell carcinoma in each) reported in 49 to 60 year old subjects and newly diagnosed, new onset (not found at baseline examination or reported as a pre-existing condition). These events were revealed at 4-6 months of treatment.*
- ***1 Probable Skin Malignancy and 1 Unclear Diagnosis (of a skin tumor surgically removed) in the OL phase:*** *1 Probable malignancy (based on the narrative, and not based on the sponsor's summary table, which indicates "possible") and1 unclear diagnosis of a skin tumor that was removed in a 23 year old subject number 0434019 (no other information relevant to the diagnosis/etiology was found, except for a past history or a "benign" tumor removal, and diagnostic information based on subject's report). These events occurred out of 360 ITT Safety OL subject with the probable case occurring in a 53 year old and both events occurring after 7 months of treatment.*
- ***Additional skin-related events*** *are described in the review and included pre-neoplastic-like events of actinic keratosis and nevi (primarily found on physical examination, while none of these events were generally found at baseline or earlier examinations). Note that these events (actinic keratosis and nevi) were diagnosed primarily by physical examination (rather than by self-subject report) and are common in the general population. It is not clear why these events were found later after treatment, instead of at baseline. Therefore, they are listed as being potential drug-related, but are not malignant neoplastic events.*
- ***1 Ductal Carcinoma of the Breast and 1 Possible breast neoplasia in the OL phase*** *(information not considered adequate on the latter event to conclude a benign non-neoplasia event) out of 295 ITT Safety female subjects (the number of 295 is based on demographic summary tables found in the original submission).*
- *Several other breast related events diagnosed according to narratives as fibrocystic disease (primarily on the basis of physical examination, several on the basis of self-report and a few by pathological examination). These events are described later in this review. These additional events were considered by the reviewer to be events that are not likely to be events of neoplasia for reasons provided later.*
- ***An additional breast malignancy (pathological diagnosis) that is not likely to be drug-related was reported in a blinded ongoing 6-month Primary Insomnia study (Study 190-050) of 303 female randomized subjects (2:1 randomization ratio of all male and female subjects to ESZ or placebo).*** *This subject was being evaluated for a "lump" in breast (found approximately 9-10 months prior to the study) and ultimately had a biopsy performed after approximately 3 months of treatment (study drug is blinded) that was positive for a malignancy, such that the*

subject withdrew from the study. Given the past history, it is likely that this is not a drug-related event.

- ***5 "uterine" related events that are not likely to be events of malignant neoplasia and most events were likely to be leiomyomas*** *(events are listed in the sponsor's summary table of "benign neoplastic events," of which a copy is provided in this review). Most events were probably, if not diagnosed by pathology, as uterine leiomyomas (not uncommon in women within the age of these subjects). However, 3 out of 5 "uterine fibroids" or "uterine leiomyomas" were based on self-report (which is not considered a definitive diagnosis for the purposes of this review). Yet, one subject underwent "elective" surgery and all 3 subjects were 38 to 45 years old with pre-existing related conditions. Furthermore, the nature of symptomatology and/or past history, the age of the subjects, among other factors are more consistent with more common conditions, such as fibroids women at this age. Uterine and ovarian cancers are rare and generally do not present with a history of the type of symptoms/signs described in these 3 subjects (either at the time of the events or in their past history). These subjects are described in more detail later in this review. Therefore, the events are considered as not likely to be events of malignant neoplasia.*
- ***Several isolated events of possible or probable neoplasia.*** *These events are described here, because this reviewer could not consider the event as probably benign or as non-neoplastic events.*
  - *One is subject 0450024 (one of the 3 subjects with AEs of "neoplasia" of interest identified in the Approvable Action Letter) in which the diagnosis/etiology of the nodules of the liver and the single lung nodule found on CT remains unclear, although the patient appears to be stable over a 3 year period since they were first discovered suggesting that they may not be malignant. The lung nodule was also followed by serial CTs and found to be fairly stable in size with no new lesions, no adenopathy and no other evidence of metastases (which often occurs in the brain, but also the liver) reported in the last CT 1 year after the study. When contacted three years after the study, she reported to be well, asymptomatic and unaware of plans for repeat chest CTs. However, the 43 or 44 year old subject (exact age is not clear) had a past history of smoking 1 ½ packs per day over 28 years and stopped one year prior to the study. This subject also had breast nodules identified at baseline and a renal cyst that are not likely to be related to the liver and lung events (since the lesions were reportedly cystic), although follow-up information during and after the study on these additional events could not be found.*
  - *Subject 0398013 was diagnosed by an endocrinologist as having multinodular goiter which was evaluated after the subject reported a "thyroid nodule in the left side of her neck" on Day 219 of treatment with no history of thyroid disease and normal thyroid function tests at baseline and thereafter. The diagnoses by an endocrinologist was "multinodular goiter, most probably an inflammatory process, with no apparent autoimmune process" (as stated in the narrative). The subject was 61 years old with no history of thyroid disease who after 219 days on treatment reported "thyroid*

nodule" on the left side of her neck. On physical examination it was 1 cm, non-tender and freely mobile. Thyroid function tests throughout the study were reported as normal. Ultrasound revealed an isoehoic mass occupying the "entire right lobe" and a "smaller mass" was found in the lower pole of the left lobe, of which both "were stable" upon a repeat ultrasound 6 months later. Fine needle aspirate showed colloid with follicular cells and "histiocytes and increased lymphocytes consistent with a colloid nodule." Thyroid function was normal (no values) and no thyroid antibodies were found. Given the age of this subject and the final diagnosis, provided by an endocrinologist (as described in the narrative), it is likely that this event is an isolated case.

- *Additional events that were isolated or not likely to be neoplasia include the following:*
  - *Subject 421004: Who had a "knot" sensation of her throat" recorded as a throat nodule on Day 157, that was most likely related to worsening of gastro-esophageal reflux.*
  - *Subject 04110009: diagnosed with benign bladder polyp after finding hematuria on Day 183 of ESZ treatment and underwent a work-up (diagnostic tests are not described) and dignosed on Day 260.*
  - *Subject 031703: Benign GI polyps diagnosed by endoscopic pathological examination as 1 hyperplastic polyp and 2 polyps with normal mucosa after being evaluated for worsening of intermitten abdominal pain on Day 99 of treatment (date of onset of pain could not be found and pain was accompanied with nausea, vomiting and diarrhea).*
  - *Subject 0401008: Bladder cyst (not clear how this was diagnosed) recorded on Day 226 of treatment in a 61 year old who presented with hematuria and abdominal pain (over 2 months on study drug), but the subject was able to continue in the study.*

Additional gynecological events were identified and described in the review of the original NDA, as summarized later in this review.

It is important to note that the above events were found despite stringent entry criteria, particularly in patients at risk of lung, breast and thyroid neoplasia (as described in the original NDA review and in the current submission).

Reviewer Recommendations Regarding Events of Neoplasia and Other Events Described under Item 1

Because many cases were not clear, it is recommended that consultations be obtained as described below. Furthermore, the incidence of such events that one can anticipate as a normal "background" rate in a controlled drug trial, particularly one involving stringent screening criteria for patients at risk for breast, lung and other carcinomas is not clear to this reviewer. Perhaps there is data from other controlled trials on this issue. Refer to

the review of the original NDA regarding observed incidence of neoplastic events in the development program of Sonata®, as described under Section XI.

Preclinical studies show findings of mammary gland tumors and other malignant tumors found in other organs (lung, thyroid and skin) were found, but the conclusions and recommendations drawn from preclinical studies differed among the Division and Agency team members (refer to the Pharmacology Toxicology review, the Pharmacology Toxicology Team Leader and Clinical Team Leaders Memos-to-the-File, the Division Directors and Office Directors Memos-to-the-File, for details).

It is recommended that an oncology consultant be obtained to answer questions listed below (Q).
Oncology consultant Qs:

1. *Does the consultant agree with the Clinical Reviewer's conclusions regarding the selection and enumeration of adverse events to be considered as events of neoplasia or probable neoplasia (as enumerated in the synopsis above using the strategies described in this draft review of events of neoplasia)? Note that the sponsor response appears under Clinical Comment 1 of their response submission.*
2. *Is there a signal for neoplasia or for a specific type of neoplasia, while also considering animal findings (based on this understanding of this reviewer) of mammary gland tumors and according the pharmacology toxicology reviewer possible pulmonary tumors (depends on statistical methods as to whether these tumors are considered consistent with a background rate for the species), skin tumors occurred in animals housed together but not when individually housed (tumors believed to be due to animals inflicting skin lesions that progressed to tumors, yet this Clinical reviewer does not understand why treatment groups differences were revealed), and thyroid tumors (in rats believed to be secondary to a species specific response to liver enzyme induction). Some of these findings were based on studies of only the racemic zopiclone while others were examined using eszopiclone. However, a 2 year bioassay with eszopiclone was negative for tumors but exposure to eszopiclone in this study was less than the exposure achieved in the studies showing tumors with zopiclone. Also note that the incidence of rash (also some subjects with stomatitis) and infections was higher in ESZ subjects compared to placebo subjects in clinical trials (as described in the review of the original NDA).*
3. *Is there need for further investigation? If so what studies need to be conducted (please also provide a rationale)?*
4. *If the NDA were approved what is recommended for labeling regarding the clinical data on neoplasia.*

Given the majority of events were gynecological events and not clear cut, it is recommended that a consult from the Division of Reproductive and Urological Drug Products (DRUPD) be obtained to answer questions listed below.
DRUDP Qs:

1-4. Please respond to the above questions but in reference only to gynecological events of neoplasia.
5. Is there a signal for gynecological adverse events (refer to sections above and below describing breast, uterine and other gynecological events, also refer to a summary of events described in the original review of the NDA that are also summarized in a subsection below)?
6. Is there need for further investigation for gynecological adverse effects?
7. If the NDA were approved what is recommended for labeling regarding gynecological adverse events.
8. It is recommended that a consult be obtained from the Division of Endocrine and Metabolic Drug Products, in light of the gynecological events and preclinical findings (mammary gland tumors and effects on reproductive hormones and fertility effects)?

Sponsor's Response Regarding Adverse Events of Neoplasia in the Long Term Study 190-049.

This non-italicized section summarizes findings reported by the sponsor in the current submission. The sponsor provided narratives for all adverse events (AE) that they captured in a database search of AEs of neoplasia (for the longterm Study 190-049), including narratives for the three subjects listed in the Action Letter (as above).

The sponsor categorized each AE (using methods described later in this review) that generated a summary table for each category (e.g. malignant neoplastic events, benign neoplastic events, and others). Each table lists the AEs within the given category and provides other descriptive information. Narratives for each subject for each category are also provided. Summary tables shown below were generated by the sponsor for each category of AEs.

Before examining the sponsor's summary tables below, the following briefly describes Study 190-049 and the number of ITT Safety subjects in this study. Study 190-049 was a longterm Chronic Insomnia trial with a 6-month placebo controlled double-blind (DB) phase (the ESZ group received 3 mg daily) that was followed by a 6-month open-label (OL) ESZ phase (3 mg daily). The study had 195 placebo subjects and 593 randomized ESZ subjects in the ITT Safety population of the DB phase. A total of 471 ITT safety subjects were in the OL ESZ phase, of which 360 of these subjects previously received DB ESZ (therefore, these subjects generally received 6-12 months of ESZ in the study).

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Sponsor's Enumeration and Categorization of Adverse Events of Neoplasia Captured in their Database Search for the Longterm Chronic Insomia Trial (Study 190-049)

Table 1-4 Malignant Neoplastic Events

Subject ID	Treat-ment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests/ comments	Evidence for condition pre-existing?
0433001	ESZ	Basal cell skin cancer	Skin carcinoma	Basal cell carcinoma	143 / DB	Positive pathology	Yes
0447001	ESZ	R forehead basal cell carcinoma	Skin carcinoma	Basal cell carcinoma	166 / DB	Positive pathology	No
0473037	ESZ	Cancerous basal cells (nose)	Skin carcinoma	Basal cell carcinoma	172 / DB	Clinical diagnosis/ treated topically	Yes
0460009	ESZ	Lesion on right side of nose	Skin disorder	Possible Basal Cell Carcinoma	228 / OL	Biopsy performed, pathology report not available	No
0471012	ESZ	Pain R/T left breast biopsies	Breast pain	Ductal carcinoma in situ	267 / OL	Positive pathology	No

Table 1-5 Benign Neoplastic Events

Subject ID	Treat-ment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests/ comments	Evidence for condition pre-existing?
0401006	PBO	Dysplasia of the cervix	Cervix disorder	Cervical dysplasia	139/ DB	Colposcopy	Yes
0438008	ESZ	Uterine fibroid tumors	Uterine fibroids enlarged	Uterine leiomyoma	89/ DB	Subject report	No
0409009	ESZ	Uterine fibroids	Uterine fibroids enlarged	Uterine leiomyoma	93/ DB	Surgical pathology	Yes
0456007	ESZ	Uterine leiomyoma	Uterine fibroids enlarged	Uterine leiomyoma	330/ OL	Surgical pathology	No
0458007	ESZ	Fibroid tumors	Uterine fibroids enlarged	Uterine leiomyoma	328/ OL	Surgery; pathology not available	Yes
0430006	ESZ	Uterine fibroids	Uterine fibroids enlarged	Uterine leiomyoma	267/ OL	Subject report	Yes
0471001	ESZ	Multiple small moles on face and neck	Skin benign neoplasm	Nevi	135/ DB	Clinical diagnosis	Yes
0455012	ESZ	Nevi right leg/back	Skin benign neoplasm	Nevi	303/ OL	Surgical pathology	No
0461014	ESZ	Growth on nose	Skin benign neoplasm	Actinic keratosis	162/ DB	Clinical diagnosis/ Dermatologist	No
0434019	ESZ	Pain R/T benign skin tumor removal	Injection site pain	Benign skin tumor	254/ OL	Subject report	No
0432009	ESZ	Precancer-ous skin lesion - nose	Skin disorder	Probable actinic keratosis	237/ OL	Subject report	No

Table 1-5 Benign Neoplastic Events

Subject ID	Treat-ment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests/ comments	Evidence for condition pre-existing?
0317030	ESZ	Gastric polyps; sigmoid polyps	Neoplasm	Benign GI polyps	103/ DB	Endoscopic pathology	No
0410009	ESZ	Benign bladder polyp	Bladder neoplasm	Benign bladder polyp	260/ OL	Subject report	No
0470007	ESZ	Benign cyst (L) lower lumbar area	Cyst	Lipoma	343/ OL	Surgical pathology	No
0447018	ESZ	Lipoma	Neoplasm	Lipoma	83/ DB	Clinical diagnosis	No

Table 1-6 Adverse Events Investigated and Found Not to Involve Neoplasia

Subject ID	Treatment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests
0349017	Placebo	Vaginal dysplasia	Vulvovaginal disorder	Squamous atypia secondary to HPV	80/ DB	Pathology benign
0406001	Eszopiclone	Lump left breast	Breast neoplasm	Fibrocystic lesion or adenoma	48/ DB	Mammogram, ultrasound
0473010	Eszopiclone	Worsening fibrocystic breast tissue	Fibrocystic disease	Fibrocystic breast disease	117/ DB	Subject report
0460019	Eszopiclone	Nodule in left breast	Breast neoplasm	Fibrocystic breast disease	148/ DB	Surgical pathology
0471022	Eszopiclone	Adenoma right breast	Breast neoplasm	Fibrocystic breast disease	179/ OL	Mammogram
0454003	Eszopiclone	Bilat. Breast tenderness secondary to mild fibrocystic changes	Fibrocystic disease	Fibrocystic breast disease	265/ OL	Physical examination
0087011	Eszopiclone	Fibrocystic breast changes bilateral	Fibrocystic disease	Fibrocystic breast disease	268/ OL	Physical examination
0087031	Eszopiclone	Mild Fibrocystic changes bilaterally	Fibrocystic disease	Fibrocystic breast disease	358/ OL	Mammogram and ultrasound
0087028	Eszopiclone	Fibrocystic breast changes bilaterally	Fibrocystic disease	Fibrocystic breast disease	362/ OL	Physical examination

Table 1-6 Adverse Events Investigated and Found Not to Involve Neoplasia

Subject ID	Treatment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests
0087008	Eszopiclone	Fibrocystic breasts bilaterally	Fibrocystic disease	Fibrocystic breast disease	364/ OL	Physical examination
0110001	Eszopiclone	Pain R/T endometrial biopsy	Pain	Breakthrough uterine bleeding	63/ DB	Subject report; pathology unavailable
0432002	Eszopiclone	Ovarian cysts	Cyst	Functional ovarian cyst	74/ DB	Ultrasound
0447017	Eszopiclone	Abnormal PAP	Papanicola smear suspicious	False positive PAP	275/ OL	Colposcopy normal
0447025	Eszopiclone	Cervical polyps	Cervical neoplasm	Reactive cervical polyp	277/ OL	Pathology benign
0401008	Eszopiclone	Benign bladder cyst	Bladder neoplasm	Bladder cyst	226/ OL	Subject report
0457033	Eszopiclone	Nasal polyp	Neoplasm	Inflammatory nasal polyp	166/ DB	Pathology benign per subject
0421004	Eszopiclone	Nodule in throat	Neoplasm	Globus	157/ DB	Clinical symptoms
0450024	Eszopiclone	Nodules found on right kidney; nodules found on right lung; nodules found on liver	Neoplasm	Non-neoplastic hepatic hypodensities, pulmonary nodule, and renal cyst	176/ DB	Serial CT scans and clinical follow-up times 2.5 years

Table 1-7 Adverse Events Investigated and Found Not to Be Relevant to the Analyses

Subject ID	Treatment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests/ comments
0451001	Placebo	Post ovarian cyst surgical pain	Injection site pain	Ovarian cysts (baseline event)	27/ DB	Pre-planned surgery
0439027	Eszopiclone	Post surgery pain due to dilation and curettage	Injection site pain	Normal endometrium	27/ OL	Pathology normal
0442008	Eszopiclone	Nevus to back	Skin benign neoplasm	Nevus (baseline event)	1/ DB	Physical examination

Table 1-7 Adverse Events Investigated and Found Not to Be Relevant to the Analyses

Subject ID	Treatment	AE verbatim	AE Preferred term	Final diagnosis	Days to report/ period	Confirmatory tests/ comments
0450021	Eszopiclone	Facial cyst	Cyst	Cystic acne	262/ OL	Physical examination/ active acne
0466005	Eszopiclone	Abnormal prostate biopsy	Prostate neoplasia	Benign prostatic hypertrophy	57/ DB	Pathology benign
0398013	Eszopiclone	Thyroid nodule L side	Thyroid disorder	Multinodular goiter	219/ OL	Pathology benign
0438011	Eszopiclone	Lump on palate	Mouth neoplasia	Blister on palate	26/ DB	Subject report/ resolved in 4 days
0401004	Eszopiclone	1 cm macule under right eye	Skin discoloration	Spontaneously resolved macule	135/ DB	Subject report
0432007	Eszopiclone	Skin lesion left and right facial cheek	Skin disorder	Normal skin	158/ DB	Dermatologist confirmed absence of lesion
0471016	Eszopiclone	Lesions on inner thighs Lesions on inside of arms	Skin disorder	Eczematous dermatitis or fixed drug eruption	218/ OL	Clinical diagnosis
0448021	Eszopiclone	Lip pain secondary to biopsy	Injection site pain	Sjogren's syndrome	240/ OL	Biopsy confirmed
0087014	Eszopiclone	Oral pain R/T surgery	Injection site pain	Dental surgery	340/ OL	Subject report
0451004	Eszopiclone	Left ovarian cyst; uterine mass	Cyst; uterine neoplasm	Pregnancy	61/ Post	Ultrasound confirmed intrauterine pregnancy

Note: ESZ = eszopiclone; DB = double-blind period; OL = open-label period; Post = >14 days following the last dose of study treatment.

Note: Days to report is relative to first dose of eszopiclone with the exception of Subject 0451001, where days to report is relative to the first dose of placebo.

The Sponsor's Methods for the AE Database Search and Categorization AEs of Neoplasia for Item 1 Response (which resulted in the above Summary Tables).
The sponsor searched for Preferred and verbatim terms AEs that "could potentially be related to an adverse event of neoplasm" in Study 190-049 and reviewed the case report form data and "supportive documents." Two "independent" oncologists served as consultants who reviewed "comprehensive information" of each case to make a determination if a given case was neoplasia or a non-neoplastic process. In 2 cases the oncologists differed in opinion and were asked to reach consensus. They were then asked to categorize neoplastic events on whether the cell line of origin was epidermal, endodermal or mesenchymal. Each case was then placed into one of the following categories, as defined below:

- Malignant neoplasia: "any form of cancer whether invasive or non-invasive"
- Benign neoplasia: "any clonal proliferative lesion that does not meet the definition of a malignancy, including pre-cancerous conditions.
- Non-neoplastic: Lesions that show no clonal proliferation of cells, although hyperplasia or inflammatory proliferation may be present."
- Non-neoplastic and not relevant to this analysis: Events that do not involve any type of proliferation lesion, or were clearly documented to have been present before randomization and were unchanged.

It is not clear if the oncology consultants were also involved in ultimately categorizing each AE into one of the 3 above categories.

Study 190-049 is a Chronic Insomnia study involving 6-months double-blind ESZ (3 mg/day) or placebo treatment followed by 6 months of OL ESZ (3 mg/day). Thorough screening methods including diagnostic procedures for lung, breast and thyroid neoplasia were employed on subjects at risk (as described in the review of the original submission and as described in the current submission on page 21-22 in the clinstat\clinsum.pdf file). Subjects with any history of any malignancy, except for non-melanomatous skin cancer were also excluded.

Exposure in patient years was provided as requested: 427 person years to eszopiclone and 67 person years to placebo in Study 190-049 (methods of these calculations cannot be found).

<u>More Detailed Information on A Review of Events, Reviewer Methods for Classifying events of Neoplasia, A Description of Gyencological Events.</u>
The following subsections provide more detailed information regarding the approach taken in enumerating subjects with neoplasia in Study 190-049 and enumerating these subjects relative to Drug Exposure. Additional subsections described gynecological events (some of which were reported as events of neoplasia). These subsections are italicized, since they reflect reveiwer's comments and conclusions based on the information provided in the current submission.

Drug Exposure (in Patient Years as requested in the Approvable Letter) and Reviewer Comments Regarding Exposure Expressed as Units of Patient Years. *Given the concern for a neoplasia signal, the Approvable letter requested information on exposure in Study 190-049, specifying that exposure should be expressed in person years. As requested, the sponsor provided exposure using person years. In the opinion of this reviewer, this approach is not an adequately conservative for examining the incidence of neoplasia in a controlled study (see above summary of the study design of Study 190-049). The approach of using person years in describing exposure is generally used for post-marketing data and epidemiological data in the absence of a control group and parallel prospective study design. It also is an approach generally used for large databases. Furthermore, the estimated exposure provided by the sponsor was not provided for each gender, in the case of gender specific neoplasia or neoplasia-related events (such as breast neoplasia).*

The approach that is generally employed for describing exposure in clinical trials and for other controlled studies (preclinical and clinical trials, drug and non-drug clinical trials) is to compare the treatment groups on a given dependent variable (such as incidence of an AE) using the number of subjects in each group in the denominator (or for gender specific AEs the appropriate gender is used for the denominator). One can look at the number of completers or the number of subjects in the ITT safety population. If one were to examine results even more conservatively, then an approach to consider is examining the number of events over time subjects who continue treatment over the given treatment interval (e.g. at each 3 month interval of the DB and OL phases using and observed cases approach and using the appropriate gender if an event is gender specific).

The sponsor did not use another approach, such as examining number of events at every 3 month interval of treatment using the total number of subjects (that either entered the 3 month interval or the number who completed the 3 month interval) as the denominator to determine the incidence for the given 3-month interval.

Therefore, this reviewer takes the approach generally employed for clinical trials (using the number of ITT safety subjects in the denominator, and using the number for given gender for gender specific events).

Review Strategy in Identifying Events of Neoplasia from the Sponsor's Listing of Adverse Events under Item 1 of the Submission. *This review focused on a conservative approach. Conclusions are based on a review of the narrative descriptions of the subjects rather than relying on the sponsor's categorization of events, as listed in the sponsor's summary tables. The summary tables list events in each of the sponsor's categories (e.g. neoplastic versus non-neoplastic events and benign versus malignant neoplastic events) using methods as previous described. For the purposes of this review each narrative of each of these subjects, listed in the sponsor summary tables was reviewed for characteristics that may provide some insight on the severity (neoplasia, malignancy) and causality of the events: unilateral versus bilateral events, new versus old static events, versus old exacerbated events, for risk factors for the event (e.g. OCT, HRT, age/menopausal status, and others regarding gynecological events), duration of*

treatment, among other considerations. Other characteristics were considered in assessing the likelihood of breast related events being non-neoplastic and/or non-malignant events, as described later in a subsection that focuses on gynecological events.

Another focus of this review was to examine the more common events and to enumerate events under each category by organ system (skin, gynecological event of breast, uterine and other gynecologic events, followed by other less common or isolated events). The narratives were also reviewed to assess the likelihood of an event being malignant versus benign, neoplastic versus non-neoplastic.

Because many events were breast-related, including a malignant breast neoplasia, Dr. Furlong of DRUDP was consulted regarding these events.

The above approach was employed since it is considered by this reviewer to be the most conservative approach. A more detailed description of the review strategy for the sponsor's response to Item 1 is described later.

A Detailed Description of Adverse Events Revealed by the Sponsor's Search for Events of Neoplasia in Response to Item 1

The following subsections describe the more common adverse events of neoplasia, beginning with skin neoplasia events, followed by breast-related events, uterine-related event, other gynecological events and finally a subsection on additional events involving other organ systems. This section is italicized since it reflects the reviewer's interpretation of the sponsor's results and includes reviewer comments.

Skin Neoplasias

The following enumerates skin neoplasias in each category for each treatment phase, while it is important to note that physical examinations during study visits were normal prior to the event, unless otherwise specified and all events are new, unless otherwise specified:

- *5 Events in the DB phase (593 ESZ ITT Safety subjects, 195 PBO ITT Safety subjects)*
  - *3 malignant (Basal Cell carcinoma of which 2 were confirmed by pathology) at approximately 4-6 months of DB treatment. In one case (S0473037 the PI claims that the lesion was "overlooked" on physical examinations in the study, in S0433011 the Dermatologist notes indicates that the patient was concerned about a lesion on their right thigh for 30 years prior to the study). Reviewer comments: One cannot assume that these latter two subject's malignancies were pre-existing. It is not clear how the PI knew that the lesion was overlooked in S0473037. Regarding the latter subject (S0433011), if the lesion had been present and unchanged in the previous 30 years, then one would anticipate that the lesion would have become enlarged and invasive over the previous years and one cannot rule out a conversion between benign to malignant or a progression of a pre-existing condition associated with ESZ.*
  - *1 Actinic keratosis (precancerous) on Day 162 the subject noted a growth on her nose which was diagnosed as actinic keratosis by her Dermatologist*
  - *1 Nevi (multiple face and neck nevi): reported by the subject at baseline, but not reported by the investigator on physical examinations until Visit 5 after 303 days of treatment.*

- *4 Events in the OL phase (471 OL ESZ ITT Safety subjects: 111 of which previously received DB PBO and 360 received DB ESZ)*
  - *1 Probable Basal Cell confirmed by pathology after 228 days of treatment with no pre-existing history in a 53 year old Caucasian female. The subject completed the study. Note that the sponsor's summary table listing malignant neoplasias (on page 44 in the clinstat\clinsum.pdf file) lists this event as "Possible Basal Cell Carcinoma" while the pathology reported had "probable basal cell epithelium."*
  - *1 skin tumor removal reported by the subject on Day 254 (diagnosis is not clear and information is limited).*
  - *1 Actinic keratosis (precancerous) on Day 237 by subject report*
  - *1 Nevi that was removed and found on surgical pathology to be a "melanocytic nevus, junctional type" with "no evidence of malignancy."*

Gynecological Events. *This section covers 3 types of events. First, breast-related events, then uterine-related events are described. These two types of events were the most common among gynecological events. Then a third category described below is on other gynecological events. The following descriptions and comments are based on a review of the narratives of each relevant event listed in the summary tables.*

Breast Events (refer to summary tables).
No breast events occurred in PBO subjects while a total of 10 ESZ subjects had breast events as follows:

- *One event was diagnosed as ductal carcinoma (on the basis of a pathology report)*
- *9 of breast events were diagnosed as fibrocystic disease (FBD) primarily on the basis of physical examination or on the basis of the subject's self-report.*

The enumeration of female subjects in Study 190-049 cannot be found in the current submission and as previously noted in the Clinical review of the original NDA AE summary tables appeared to provide incidence of gender specific events for the total study population rather than calculating the incidence for the appropriate gender. However, enumeration of female subjects can be found in the demographic feature summary tables and was previously described in the synopsis of Item 1, but is also described in the next paragraph (for the convenience of the reader).

The summary table on demographic features of the ITT Population (Table VIB12) in the Clinical Review of the original NDA shows that 373 out of 593 subjects were women in the DB ESZ group of the DB phase and 125 out of 195 DB PBO subjects were women. The number of women in the OL phase was 295 out of 471 subjects in which 221 of these women had previously received DB ESZ and 74 women previously received PBO.

Based on a communication with Dr. Lesley Anne Furlong in the Division of Reproductive and Urological Drug Products (at approximately 10:15 am on 6/30/04), Dr. Furlong indicated that given the prevalence of breast cancer in the general population (approximately 10%) that a single case of breast neoplasia in a study such as Study 190-

049 is not unexpected, despite that the study screened women for breast cancer (women with risk factors were required to have a baseline mammogram within the previous year).

Dr. Furlong also explained that while it is unclear if fibrocystic breast disease is a risk factor for breast cancer, this condition is very common in women in the reproductive years and can continue during post-menopausal years taking HRT. Furthermore, this FBD is know considered by many experts in the field to be a normal variant in women of the reproductive years, instead of the condition representing a pathological condition or a disease. Consequently, the incidence of FBD in Study 190-049 is not unexpected, particularly in the context of a clinical trial in which subjects are more closely monitored. Dr. Furlong also clarified that fibroadenoma (which was revealed in one subject 0460019) is benign.

Since FBD is a bilateral condition, a unilateral mass detected on physical examination is not as likely to be FBD, such that the differential diagnosis should include neoplasia. One of the 4 unilateral events described (S0471022) in this review is of potential concern to this reviewer (the other 3 subjects either had a transient condition, biopsy was negative for malignant neoplasia, or years later the subject was contacted and reported repeat mammograms showed evidence for a cyst). Even if this single case of potential concern, this single case together with the confirmed malignant case represents an incidence of 2 out of 373 or 295 women in the DB and OL phases, respectively which is still not unexpected, based on the prevalence of breasts cancer in the general population that is not generally monitored as closely as in a clinical trial. Even though women at risk were screened in Study 190-049, this incidence is not sufficient to in itself provide evidence for a role of the study drug in these events. Furthermore, the development of neoplasia generally requires decades to develop after exposure to a carcinogen.

Despite the above conclusions, one must also consider a drug-related progression or conversion from pre-neoplastic to neoplastic events, particularly in light of preclinical evidence of mammary gland tumors associated with the drug, as described in the Pharmacology Toxicology review of the NDA.

The following paragraphs provides more detailed descriptions of the breast-related events that were either diagnosed as malignant (S0471012), bilateral and unilateral breast events.

<u>Malignant ductal carcinoma in S0471012:</u> This is the only subject was categorized "malignant" that was a biopsy confirmed ductal carcinoma, in situ, in the left breast on Day 267 of ESZ treatment in a 54 year old female with past history of Premarin use and positive history of calcification deposits in the left breast (appears to be by self-report). The subject had a normal PE at baseline. Mammography was conducted at approximately 147 days of ESZ treatment that revealed 5-10 new lesions ("microcalcifications") compared to a pre-study mammogram conducted at approximately 7 months prior to ESZ treatment. While this subject had a pre-existing history for breast calcifications, new lesions were revealed at 147 days of treatment (it is

not clear why mammography was conducted at this time) and a biopsy revealed malignant neoplasia, such that one must consider a potential role of ESZ. One must consider an exacerbation of an undiagnosed malignant neoplasia or a conversion from benign (or non-neoplastic lesions) to malignant neoplasia associated with ESZ treatment.

Other Breast Events. No breast events were listed in the summary table for events categorized by the sponsor as "benign neoplasia." However, 9 breast events (all were diagnosed as fibrocystic disease) were categorized as non-neoplastic events (on the basis of the diagnosis in which the sponsor indicates that 95% of FBD do not represent clonal proliferative processes).

Out of the 9 cases of fibrocystic breast disease (FBD) which were diagnosed primarily by physical examination (PE), 5 cases were bilateral breast events (generally bilateral due to bilateral breast tenderness or pain, or determined by PE) that occurred in subjects over 42 years old (except for a 29 year old, described later) with a history of potential risk factors (OCT, HRT, perimenopausal or post-menopausal, and others). Only one of the 9 cases was a biopsy confirmed diagnosis that revealed some tissue sections "suggestive" of "early fibroadenoma" in a subject with unilateral breast involvement, as described later.

Although the majority of events were bilateral which is more suggestive of FBD and the majority of these subjects had risk factors, it is important to note that the events were primarily new events (new events in 6 subjects, a worsening of a pre-existing condition in 2 subjects, and in 1 subject, it was not clear if it reflected a worsening of a pre-existing condition). Note that most subjects had a normal baseline PE.

All but one of the events occurred after approximately 4-6 months of ESZ treatment in 3 subjects (approximately 4, 5 and 6 months in 1 S, respectively) and after approximately 9 to 12 months of ESZ treatment in 5 subjects. Only one S had a shorter exposure of only 48 days with a unilateral left "breast lump" described later. Therefore, the potential role of the drug, in appearance and/or worsening of these bilateral breast events requires further consideration.

The Unilateral Breast Events. The following describes unilateral events, since unilateral events are less likely to be a benign condition. As already mentioned these events were listed by the sponsor as being diagnosed as FBD. Unilateral "non-neoplastic" breast events were reported in 4 subjects (not counting the 1 malignant breast event, previously described). Three of these four unilateral events were newly detected/diagnosed events (no past history of the event) and 1 event was a transient worsening of a previously diagnosed FBD (by subject report). 3 events (in each subject respectively) occurred at Days 148, 179, 117, respectively, while for fourth event occurred at Day 48 treatment (a mammogram and ultrasound was performed after the subject detected a "lump" in her left breast on Day 48 of ESZ in this 57 year old with risk factors and who's primary care physician diagnosed as having FBD with benign lesions).

Since all the events were new events, as well as unilateral, the potential role of the drug must be considered further. However, the one probable exception is the event

that occurred at day 48 of treatment (0406001). This subject was recently contacted by the sponsor (approximately 3 years after she withdrew from the study) and the subject reported that a repeat mammogram was performed (no dates) that showed no changes and that she had a "cyst...confirmed on a mammogram." One of the other 4 events was a transient worsening for 3 days at Day 117, by self-report that resolved spontaneously in which the subject completed the study (0473010). The two remaining and unexplained unilateral events require further consideration as potential neoplastic events. Therefore, these events are described in more detail in the following:

- *S0460019 with no history of FBD or breast neoplasia, had a biopsy (not clear why it was performed) on Day 148 of ESZ and found to have FBD, but also, some tissue samples were suggestive of "early fibroadenoma." This subject was 63 years old. Given the age of this subject and based on a verbal consultation with Dr. Furlong (as previously described), fibroadenoma is benign.*

- *S0471022 had a 2x3 cm "breast nodule" (not stated how this was measured and found) on Day 179 of treatment. Approximately 1 month later the nodule was 2x2 cm, but the method for measuring the size and detection and the validity of this measurement is not known. This was a new event in a 44 year old who was taking OCT. This event is of greater concern, since it involves a single nodule and the diagnosis remains unclear (no pathology report or other clear evidence that the event is not a neoplastic event).*

Aside from the concern of mammary gland neoplasia, the above events may be reflecting a drug-related effect on development or worsening of FBD, such that a DRUDP consult is recommended (as previously discussed).

Uterine Events

A total of 5 ESZ subjects (38-56 years old) and no placebo subjects had "uterine (or "fibroid") tumors, enlarged" (Preferred terms) that were diagnosed as "uterine leiomyoma" as follows:

- *3 subjects underwent surgery (2 with pathology reports available, confirming the diagnosis)*
- *The diagnosis in 2 subjects was self-reported (it is not clear how the diagnosis was made).*

Refer to summary tables for the subject numbers of the above subjects. While 4 out of 5 had pre-existing conditions or risk factors (e.g. history of menstrual disturbances, menopausal or peri-menopausal, HRT in 2 subjects), 4 out of 5 subjects were newly diagnosed with uterine leiomyoma. Also note that most or several risk factors are also risk factors for related neoplastic events.

Only 2 subjects had pathology reports available confirming the diagnosis. Another subject underwent elective surgical treatment of a pre-existing, but stable condition of uterine fibroids with dysfunctional bleeding (no pathology report and it is not clear why she underwent surgery after 328 days of treatment).

It is difficult to confirm the diagnosis in at least the 2 remaining subjects, given that they self-reported their diagnosis (one subject reported receiving no treatment and the other subject reported treatment with progesterone).

Overall, the nature of symptomatology and/or past history, the age of the 3 non-pathologically diagnoses subjects, among other factors in the subjects were more consistent with more common conditions, such as fibroids women at this age. Uterine and ovarian cancers are rare and generally do not present with a history of the type of symptoms/signs described in these 3 subjects, as described in the narratives (either at the time of the events or in their past history).

The timing of the events relative to treatment was after approximately 3 months of treatment in 2 subjects (1 subject self-reported her condition and the other subject had surgery with a pathology report) and approximately 9-11 months of treatment in 3 subjects (2 subjects underwent surgery of which one had a pathology report available, 1 subject self-reported her condition).

While the events appear to be due to a common benign condition in women in this age-group, a role of eszopiclone must be considered in at least exacerbating a pre-existing condition or in development of fibroids in patients at risk for fibroids. In the absence of pathology confirmed diagnosis in at least 2 of the subjects (the subjects who self-reported their condition and did not undergo surgery), then the accuracy of their diagnosis is open to question.

In addition to benign leiomyomas noted on the pathology reports that were available in 2 of the 3 surgically treated subjects, the following was also noted in the reports: adenomyosis, proliferative endometrium or cystic endometrial hyperplasia in both subjects and a benign paratubal cyst of the left fallopian tube in one subject.

Another uterine related events was "breakthrough bleeding" in a perimenopausal or recently diagnosed menopausal woman (onset approximately 3 months prior to study entry) in a 63 year old who self-adjusted her HRT and underwent endometrial biopsy and later discontinued the study drug due to "daytime exhaustion and impaired cognition."

Other Gynecological-related Events.

Two placebo subjects (in the DB Phase) had gynecological events of "vaginal dysplasia" of "squamous atypia secondary to HPV" (a pathology diagnosis) in one subject and of cervical dysplasia diagnosed on colposcopy in the other subject.

The following lists ESZ subjects with gynecological related events, listed in the summary tables, but are not already described in this review:

- *Subject 0432002 presented with abdominal pain (on Day 74 of treatment) and an ultrasound revealed an ovarian cyst. The subject withdrew from the study.*
- *Subject 447017 had a false positive PAP smear.*
- *Subject 0447025 was diagnosed as having "chronic inflammation with epithelial atypia" on pathological examination of cervical polyps (an initial PAP smear showed "low grade squamous intra-epithelial lesion).*

Additional Reviewer Comments Regarding Female Gynecological Events.
It is important to note that the sponsor's summary tables that include breast-related and other female gynecological events regarding AEs of neoplasia do not capture other female gynecological events. Furthermore, the sponsor's summary AE tables in the original NDA submission (see Clinical review) appeared to show incidence of gender specific AEs using the total number of subjects in the denominator, rather than calculating the incidence for the appropriate gender. A total of 72 subjects in the DB phase had urogenitial events compared to 14 placebo subjects (gender appropriate incidence cannot be found and primarily involved female breast-related, menstrual/uterine/vaginal bleeding type of events that were not captured in the summary tables in the current submission.

The following outlines these AEs and the gender specific incidence of each of the more common AEs was calculated by this reviewer using the enumeration of female subjects in the sponsor's demographic summary table (refer to the Clinical review of the original NDA for a copy of the summary table):

- *Dysmennorhea: 16/373 ESZ females (4.3%) compared to 4/125 Placebo females (0.3%)*
- *Menorrhagia or Metrorrahiga: 5 ESZ females (1.3%), 2 placebo subjects (1.6%)*
- *Vaginal or uterine hemorrhage: 4 ESZ females, no placebo subjects*
- *Uterine enlargement: 2 ESZ females and no placebo subjects*
- *Breast pain in 9 ESZ subjects (2.4%) and 0% placebo*
- *4 ESZ subjects had additional breast related AEs compared to 0 placebo subjects that included 1 mastitis, 1 lactation, 2 breast enlargement or engorgement.*

Refer to a more detailed and complete discussion of gynecological related events and safety findings relevant to the gynecological and reproductive endocrine system. Most of the above events are not likely to reflect neoplasia since uterine, ovarian and breast neoplasias generally do not present with these type of events. While neoplasia involving the reproductive tract (uterine/cervical/ovarian) neoplasia can present with dysmennorhea, this is generally not present in the absence of other symptoms and signs and patients are generally asymptomatic until the neoplasia has already metastasized and is in more advance stages.

Breast neoplasia more commonly presents with a unilateral single mass found by the patient upon self-examination and is generally not painful (while FBD is generally bilateral, can be painful and generally involves multiple cystic lesions that can be palpated as multiple tumors). Breast neoplasia also does not generally present with the complaint of breast engorgement/enlargement, mastitis or lactation and does not generally involve both breasts.

A Reanalysis of the Incidence of Gender Specific AEs Reported in Chronic Insomnia Trials

Upon request the sponsor re-analyzed data on the incidence of gender specific AEs using the appropriate gender for the denominater (in the original NDA they used the entire sample size of both genders to calculate these AEs).

The following are new findings on the basis of the sponsor's re-analyses in Chronic Insomnia trials (now using the appropriate gender for the denominator for calculating the incidence and as described in the recent 9/30/04 submission):

The 6-week placebo controlled study, Study 190-046:

- Dysmennorhea was 0%, 3% and 0% in placebo, 2 mg and 3 mg daily eszopiclone (ESZ) groups. This does not capture other types of menstrual irregularities.

The 6-month DB phase of Study 190-049 (incidence of placebo and the 3 mg/day ESZ groups shown, respectively:

- Breast pain: 0%, 2.4% (also a few more ESZ subjects with breast enlargement and engorgement compared to placebo but <1%, each)
- Vaginal moniliasis: 0.8%, 2.4%***
- Vaginitis: 0%, 1.1%***

***As previously described in this review, there is a signal for greater incidence of infections, primarily upper respiratory, but in the longer term trial other infections show slightly greater numerical incidence rates in ESZ subjects compared to placebo.

Reviewer comments on the above new findings: *The reanalyses revealed new treatment group differences as described above. Some AEs that are similar in nature may be more appropriately combined, in which case additional treatment group differences or greater differences may be revealed. Also, note that some gender specific events found to show treatment group differences in the longer term study, involved events that are inflammatory in nature or fungal infectious (vaginitis and vaginal moniliasis). Item 2A below focuses on AEs of infections but may not capture gender specific AEs, such as those above. A consult from the Division of Reproductive Urological Drug Products was requested, as previously described and their input is pending at the time of this writing. The consultant was provided with the above results and informed of the recent 9/30/04 submission.*

Revised Labeling Proposed by the Sponsor to Reflect New Gender Specific Findings Provided in the 9/30/04 Submission.

The sponsor revised Tables 1 and the "Other Events Observed..." section of proposed labeling (as shown in the labeling\other.pdf file of their 9/30/04 submission). Since Table 1 in labeling is provides the incidence of AEs in Study 190-046 then the sponsor revised labeling in the 9/30/04 submission now shows results on dysmennorhea (as shown above). The new gender AE findings of the longer term trial, Study 190-049 that were provided in the 9/30/04 submission are not captured (included) in the Adverse Reactions section of proposed labeling, since a summary table of AEs in this study was not included in labeling in the Approvable Letter version of labeling. Therefore, any additional gender specific events are included in the sponsor's revisions under the "Other Events Observed...."

As previously described, a consult from the Division of Reproductive Urological Drug Products was requested and is pending at the time of this writing.

Other Neoplasia Events of the Throat, Pharyngeal/Oral Mucosa, Gastrointestinal Mucosa and the Bladder:

- *DB Phase*
  - *Subject 421004: Nodule in throat was recorded, but later the diagnosis was changed to globus. The subject has a history of GERD and complained of a "knot" sensation of her throat on Day 157 that increased with swallowing and also had worsening of her GERD. She had also started Lipitor® approximately 2 weeks before the event.*
  - *Subject 04110009: Benign bladder polyp: a 40 year old female with a history of frequent UTIs had microscopic hematuria (reported as an AE) that was revealed on a routine urinalysis on Day 183 (per protocol). She was evaluated by her urologist and she was given the diagnosis of benign bladder polyp after a work-up (diagnostic tests are not described). The event was reported on Day 260.*
  - *Subject 031703: Benign GI polyps diagnosed by endoscopic pathological examination as 1 hyperplastic polyp and 2 polyps with normal mucosa. This subject was evaluated for worsening of pre-existing abdominal pain on Day 99 of treatment (date of onset of pain could not be found) that was accompanied with nasea, vomiting and diarrhea, the subject was hospitalized and underwent a GI work-up. She also was found to have adhesions (history of hysterectomy, cholecystectomy and endometriosis).*
  - *Subject 0457033: Inflammatory nasal polyp with benign pathology per subject's report who had a history of seasonal hay fever and "sinus problems."*
- *OL Phase*
  - *Subject 0401008: Bladder cyst (not clear how this was diagnosed) recorded on Day 226 of treatment in a 61 year old who presented with hematuria and abdominal pain (over 2 months on study drug), but the subject was able to continue in the study.*
  - *Subject 0398013: Left thyroid nodule diagnosed by an endocrinologist as "multinodular goiter, most probably an inflammatory process, with no apparent autoimmune process" (as stated in the narrative). The subject was 61 years old with no history of thyroid disease who after 219 days on treatment reported "thyroid nodule" on the left side of her neck. On physical examination it was 1 cm, non-tender and freely mobile. Thyroid function tests throughout the study were reported as normal. Ultrasound revealed an isoehoic mass occupying the "entire right lobe" and a "smaller mass" was found in the lower pole of the left lobe, of which both "were stable" upon a repeat ultrasound 6 months later . Fine needle aspirate showed colloid with follicular cells and "histiocytes and increased lymphocytes consistent with a colloid nodule." Thyroid function was normal (no values) and no thyroid antibodies were found. Given the age of this subject and the final diagnosis, provided by an endocrinologist (as described in the narrative), it is likely that this event is an isolated case.*

Other individual subjects are listed in the summary tables. One subject had a eczematous dermatitis (0471016) that was likely to be drug-related but no involving neoplasia. Others subjects are either previously described in this reviewer or their

narrative revealed other likely causal factors and/or the nature of the events were not likely to be drug-related or to involve neoplasia and/or the event was not unusual or remarkable given the demography of the population.

A breast malignancy in a subject in the blinded ongoing 6-month Chronic Insomnia study (Study 190-050). Reviewer Comment Regarding this SAE: *Given the pre-existing findings and a fairly short treatment duration in which the study drug remains blinded, it is likely that this event is not drug-related. However, consideration needs to be given to a potential progression or conversion from a benign to a malignant tumor that may be drug-related.*

Reviewer Labeling Recommendations Regarding Results of Clinical Item 1.
Input for the Division of Oncology Drug Products and the Division of Reproductive Urological Drug Products was requested and input is pending at the time of this writing.

Clinical Item 2 A: Incidence of Infection

Approvable Letter Comment

It appears that there is an increased incidence of both "Infection" and "accidental injury" on drug compared to placebo, but you have not adequately examined these issues.

Specifically, we note that there are a number of events that could reasonably be considered as "Infection" that you have not included under this term (for example, pharyngitis, bronchitis, etc.). In addition, you need to examine all cases and classify appropriately; viral syndromes are not necessarily the same as an abscess. Please re-examine your database and identify all possible verbatim terms that could reasonably be considered to represent an infection, and perform appropriate analyses of the comparative incidences of these events Similarly, please examine your database for all possible verbatim terms that coulc reasonably be considered to represent accidental injury (for example, laceration, bruising etc.) and perform the appropriate comparative analyses.

Sponsor's Response to Item 2A. The sponsor reanalyzed the incidence of AEs of infection for the following Chronic Insomnia trails: two (2-week) elderly trials (190-047 and -048), the 6-week non-elderly trial (190-046) and the 6-month DB phase of the non-elderly adult study, 190-049. The sponsor examined verbatim terms for any infectious type terms and categorized the AEs into one of three categories: viral, bacterial and fungal based on the verbatim term (e.g. flu syndrome was categorized as viral). In cases where the disease process was not clear, then the sponsor classified the event by the treatment administered (e.g. antibiotic treatment was categorized as bacterial). These categorizations were conducted in a blinded fashion. The sponsor also referred to the literature for justification for some of the classifications.

Reviewer Comment on the Sponsor's Classification Methods for Adverse Events of Infection in Response to Item 2A. *Examination of the Preferred and verbatim terms under each disease process category (bacterial, viral and fungal) as provided in the submission generally appear to be reasonable, but the classification system chosen by the sponsor presents serious limitations of the results. In many cases, the verbatim term is unclear as to the type of infection that was involved. In these cases, the sponsor indicates*

that they referred to the treatment that was given, as a means of classification for cases that were unclear, which appears to be for most cases. However, treatment does not often accurately reflect the type of infections process, in the absence of diagnostic tests. For example one of the common events were upper-respiratory related (e.g. bronchitis, "cold," and others). Furthermore, if no treatment was given they were classified as viral. As described later, most events were classified as viral and not bacterial. However, many of these cases may have involved bacterial infections or secondary bacterial infections (secondary to an underlying viral infection but resolved without antibiotic treatment).

Another serious limitation in the interpretation of the results using the sponsor's classification system is that some events may not fit into any of the three categories. That is, events may have involved non-viral, non-bacterial and non-fungal inflammatory processes. Thus, an infectious process that involved a Type IV inflammatory response (involvement of eosoniphilia, allergic type responses) and other types of inflammatory responses either may not be included or are miscategorized under one of the sponsor's categories. For, example it is not clear if rashes were included and how they were categorized. However, as described later treatment group differences in rashes and related events (pruritis, urticaria and others) were observed in longer term trials (as noted in the review of the original NDA).

Finally, one assumes the verbatim terms are accurate. For example flu syndrome may have instead have been a different type of infection (hepatitis, bacterial enteritis such as "food poisoning" among others).

Results of the Two 2-week Elderly Studies and Reviewer Comments (Part of the Sponsor's Response to Item 2A)

As previously noted in the Clinical Review of the original NDA, the 2-week elderly studies did not show treatment group differences on the incidence of infections in the ESZ group compared to the PBO group. The current submission shows similar results. Failure to show treatment group differences in these 2-week studies may be due to the shorter duration of treatment and/or monitoring compared to longer term trials of 6 weeks and longer conducted on non-elderly patients. These longer term studies showed treatment group differences.

Results of the Longer Term Non-elderly Studies in Response to Item 2A. The longer term trials (as previously noted in the original review) showed either a numerically greater incidence of all infection-related AEs (the 3 disease process categories, combined) in ESZ patients compared to PBO subjects, as follows:

- Study 190-046 (6-week study): 15% and 23% in PBO and ESZ groups, respectively
  By dose-level: 21% and 25% in the 2 mg and 3 mg ESZ groups, respectively
- Study 190-049 (6-month DB phase): 28% and 39% in PBO and ESZ groups, respectively.

The majority of infections in both PBO and ESZ groups in each of the above 2 longer term trials were in the viral category and only a few events were categorized as fungal

infections. The largest numerical treatment group differences were observed for infections under the viral category (Study 190-046: 13% in PBO and 19% in ESZ subjects, Study 190-049: 19% and 29%, respectively). The ESZ groups also showed numerically greater incidence in bacterial and fungal infections, but the differences were numerically smaller (Study 190-046: bacterial; 3% in PBO and 4% in ESZ, fungal; 0% and 2%, respectively, Study 190-049: bacterial; 12% and 15%, respectively, and fungal; 1% and 3%, respectively).

The sponsor provides the incidence of the "viral" infection Preferred Terms (bronchitis, conjunctivitis, fever, flu syndrome, among others) for Study 190-049 but not for Study 190-046 and not for the other two categories (bacterial, fungal). Upon inspection of the summary table, below the majority of events categorizes as "viral" were "infection" (77 out of the 170 ESZ subjects with AEs under this category). The verbatim terms for most of these events under "Infection" included the term "cold" (i.e. common cold, head cold, among others). Consequently, the majority of these events appear to be verbatim term events of upper respiratory infections. Pharyngitis was among the AEs categorized as viral and consisted of 49 of the viral AEs in the ESZ group. However, bacterial events occurred in 90 of the 232 ESZ subjects with AEs of infection in Study 190-049. It is not clear what these events represent, since a break down of the events were not provided in the table below.

Table 2A-6 in the submission
Incidence of Viral Infection Preferred Terms Classified in 190-049

Event	Placebo N (%)	All Active N (%)
Bronchitis	1 (0.5)	10 (1.7)
Conjunctivitis	1 (0.5)	2 (0.3)
Fever	1 (0.5)	12 (2.0)
Flu Syndrome	9 (4.6)	16 (2.7)
Herpes Simplex	0 (0)	3 (0.5)
Herpes Zoster	0 (0)	1 (0.2)
Infection	11 (5.6)	77 (13.0)
Laryngitis	0 (0)	3 (0.5)
Mouth Ulceration	2 (1.0)	1 (0.2)
Pharyngitis	9 (4.6)	49 (8.3)
Rhinitis	2 (1.0)	12 (2.0)
Sinusitis	6 (3.1)	4 (0.7)
Ulcerative Stomatitis	0 (0)	3 (0.5)
Viral Infection	3 (1.5)	12 (2.0)

Reference: EOT Table 2.1.4

Reviewer Comments, Conclusions and Recommendations Regarding Infection AEs (Item 2A).

It is difficult to interpret the results, for reasons previously described. Any treatment group differences observed on the basis of these analyses and on the results described in the original NDA review, occurred in the longer term studies, 190-046 (6-week study) and 190-049 (6-month DB Phase of this study).

It is more informative to examine infections by site of infection (e.g. by organ system). Also note that in the incidence of "body as a whole" infections in the DB phase of Study 190-049 was 7% in placebo compared to 16% in ESZ subjects. When all AEs of infection described in the current submission are enumerated the incidence for all AEs of infection is 28% compared to 39%. Similar to these observations are the results of the 6-week study in which the incidence of infections under body as a whole is 3, 5%, and 10% in placebo, 2 mg and 3 mg ESZ groups, while the above reported incidence of AEs of all types of infections is 15% in placebo and 23% in all ESZ subjects.

The summary tables did not provide a clear breakdown of the events such as events under "infection." However, end-of-text table 2.1.4 in the clinstat\clinsum.pdf (starting on page 195) shows the breakdown by Preferred and Verbatim terms for each infection-type category (viral, bacterial and fungal categories for the 2-week studies, the 6-week study (190-046) and the longer term study 190-049 (all of Chronic Insomnia patients).

Upon visual inspection of the above-mentioned, Table 2.1.4 in the submission, the longterm studies (190-046, 190-049) showed the following results. The majority of events that showed at least a numerically greater incidence in ESZ subjects compared to placebo, and the largest treatment group differences appeared to generally involve the upper respiratory system infections (such as pharyngitis, cold and other related verbatim terms).

Most of the upper-respiratory infection events (verbatim term events) in the long term trials were categorized as viral infections, although it is not clear from the verbatim terms in almost all cases, how this categorization was made. The sponsor indicated that in unclear cases they relied on the treatment given and if no treatment was given they categorized the event as viral. This method of categorization requires a number of assumptions, such that the events could have still involved bacterial infections or secondary infections and the absence of treatment does not infer that the infection was viral, among other limitations in this methodology. Unfortunately, it is difficult to develop a reliable method, retrospectively, to differentiate bacterial from viral and other types of inflammatory responses (unless specific diagnostic tests were performed, which is not likely in many cases, such as patients complaining of a cold).

In addition to the above observation on upper respiratory events under the viral category observed in the two longterm trials, additional group differences were observed in the longest study, Study 190-049 (6 month DB phase), as described in the following paragraphs.

While, treatment groups in Study 190-049 were similar in the incidence of total events in the "bacterial" category (24 out of 55 placebo subjects and 91 out of 232 ESZ; 12% and 15%, respectively), a numerically greater incidence was observed in ESZ compared to placebo subjects on specific Preferred Term categories within the overall "bacterial" category, as follows. The majority of the "bacterial" events were upper respiratory-related events (pharyngitis, sinusitis and otitis media) in which the ESZ subjects showed numerically greater incidence than placebo subjects of each these Preferred term categories than placebo subjects. The nonspecific Preferred Term of "infection" under the "bacterial" category also showed numerical groups differences. A

total of 21 of the 91 ESZ subjects with AEs under the Bacterial infection category were AEs of this non-specific Preferred Term of "infection" compared to only 2 placebo subjects in this category (1% placebo, 4% ESZ). These AEs consisted of a wide variety of nonspecific verbatim terms such as "infection" of an area of the body (e.g. groin, toe, molar, toe nail, skin and others). A total of 2 placebo and 13 ESZ subjects had AEs of urinary tract infection or cystitis (Preferred terms) under the bacterial infection category (1%, 2%).

Fever showed small numerically greater incidence in ESZ subjects compared to placebo in Study 190-049 (1 and 2%, in placebo and ESZ groups, respectively). This adverse event was categorized as viral for unclear reasons.

In conclusion, based on the above observations, infection AEs are greater in ESZ compared to placebo subjects in 6 week and longer trials, that was not observed in shorter trials (2-week trials) in which the majority involved upper respiratory infections. However, it is not clear if the infections were bacterial or viral, since this was not systematically examined in the trials. In the 6-month trial other types of infections involving other organ systems and/or were nonspecific (fever, otitis media, skin, toe, tooth and other related areas, urinary tract infections and others) also showed a greater incidence in ESZ subjects compared to placebo (generally ≤4% in ESZ subjects compared to 0-1% of placebo subjects).

Review of Incidence of Infections Provided in a 9/30/04 Submission
Upon request, the sponsor reanalyzed the incidence of infections for the 6-week and 6-month DB phase studies (190-046 and 190-049) using results of Table 2.1.4 (described above) in which data from the 3 subcategories were combined (combined data of viral, bacterial and fungal subcategories). A visual inspection of the results provided in the end-of-text-table in the 9/30/04 submission revealed similar observations to those previously described (refer to previous paragraphs).

Reviewer Labeling Recommendations Regarding Item 2A on Incidence of Infections
If the NDA is ultimately approved at the Agency level, then the following are recommendations for labeling regarding observations on AEs of infection.

It is recommended that results of the longer term trials (6 week and 6-month trials, 190-046 and 190-049) on the incidence of infections (without subcategorizing events by subtypes of infection) be described in labeling. This description should not only described upper respiratory infection, but also other infections observed in the longer term trial 190-049 that showed a numerically greater incidence in the ESZ group compared to placebo (refer the review of the original submission and to results provided in 9/30/04 for the actual incidence of events).

Appropriate sections of labeling should also state that the incidence of infections in elderly was not evaluated for treatment periods beyond 2-weeks (note that Chronic Insomnia longer term studies had the exclusion of elderly subjects as one of the eligibility criteria).

Refer to previous reviewer comments regarding AEs that may be allergic type inflammatory responses or other types of inflammatory responses that do not appear to be captured by the sponsor's analyses of AEs in the current submission or in the 9/30/04 submission. Note that results described in the original NDA review showed that the incidence of rash or related events (pruritis, urticaria and others) was greater in ESZ compared to placebo subjects in the 2-week elderly trials and the longer non-elderly studies, Studies 190-046 ND -049. Also some adverse dropouts were due to these type of events (refer to the original NDA review). It is important the labeling reflect these observations, as well.

Also refer to the final section of this review that provides additional labeling recommendations.

One key recommendation provided in the final section of this review is regarding language for the Precautions section. This section of labeling should have a paragraph that cautions the use of the drug in patients with pulmonary diseases (such as chronic obstructive pulmonary and others, in other patients at risk for pneumonia). Since the infection signal also appears to include additional types of infection in the longest trial, then these infections should also be briefly described in labeling under Precautions. The potential risk for not only respiratory infections but also other infections in immunosupressed patients should also be included in this subsection under Precautions (see the final section of this review for further comment and recommendations).

On a final note regarding the signal for upper respiratory infections with longer term treatment, the following observations regarding SAEs and adverse dropouts (ADOs)are noted. None of the SAEs and ADOs in the completed clinical Chronic Insomnia trials described in Section VIII of the review of the original submission were due to pneumonia. However, 2 SAEs of pneumonia are described for ongoing blinded trials described in Section IV of this review on the Safety Update Information. Both of these SAEs were associated with pre-existing conditions, although one should consider a potential contributory role of the drug, particularly in light of the above upper-respiratory-infection signal, assuming that the blinded drug in these 2 subjects was ESZ (studies are blinded and ongoing).

Clinical Item 2B: Incidence of Accidental Injury

The sponsor was asked to perform an analysis of their verbatim terms that could reasonably reflect accidental injury events (a copy of the Approvable Letter comment was provided under Item 2A, above).

Sponsor's Response to Item 2 B. The sponsor determined the incidence of preferred terms of accidental injury combined with verbatim terms suggestive of accidental injury (bruises, lacerations, sprains, strains, abrasions, "pulled muscle," among others) for the same studies analyzed for infections (see above Item 2A).

Results and Reviewer comments of the results are as follows. The results generally show small or unremarkable treatment groups differences for the two, 2-week elderly trials (data from the 2 trials was pooled), the 6-week Study 190-046. Study 190-049 (the 6-month DB phase) showed the greatest numerical difference between placebo and ESZ groups in the incidence was 6.2% compared to 10.1% in each group, respectively.

Since the elderly trial was only for 2-weeks of treatment, it is difficult to determine how elderly subjects compare to non-elderly adults subjects. The adult trials ranged from 6 weeks to 6 months in which treatment group differences were more apparent in the study with 6- months of DB treatment. Hence, it is important to note this in labeling as recommended later in this review.

The sponsor also analyzed the incidence of falls (verbatim terms of falls) and reported the following results:

- *Elderly trials, combined (190-048 and -047): 0.5% PBO, 1.4% (3 subjects) in 2 mg/day ESZ groups (no subjects out of approximately 100 subjects receiving 1 mg had falls reported as an AE)..*
- *6-week Study 190-046: 0% and 0% in placebo and 3 mg/day groups.*
- *6-month DB phase of Study 190-049: 0.5% and 0.8% in PBO and 3 mg/day ESZ groups, respectively.*

The results of the analyses of events using verbatim terms to capture more events that may reflect accidental injury did not reveal remarkable treatment group differences on accidental injury, combined with other verbatim terms that are suggestive of accidental injury. However, these analyses can only be considered preliminary. For example, verbatim terms included in the analyses is likely to include terms that would not reflect an accidental injury or a type of injury that would more likely be associated with the drug (e.g. a pulled muscle may reflect that a subject exercised the muscle too much).

The incidence of falls is low in all trials, generally <1% and results on the incidence by treatment group in each of the trials.

The Clinical Review of the original NDA describes slightly greater incidence in ESZ groups in these trials, for the Preferred Term AEs of accidental injury (without including other possibly related terms or verbatim terms). In Study 190-049 3% of ESZ compared to 0% PBO subjects had this AE. In the SD 1-7 day, day-time trials conducted in healthy subjects (data from these trials were combined), the incidence was 2.2% for the 3 mg and ≥3.5 mg dose-levels compared to 0% for the 1 mg dose-level and PBO subjects. More remarkable results were observed upon subcategorizing subjects with accidental injury (Preferred terms) by those with AEs of the CNS system (as conducted by the sponsor in their 120-day update report). These results of the 120-day update report analyses can only be considered preliminary given the small cell sizes for subjects with both CNS. Furthermore, the temporal relationship between the CNS AE and the accidental injury AE is not clear. The results of the two 2-week elderly trials, combined (190-047 and -048) described in the original NDA review showed an incidence of 1%, 0% and 3% in the placebo, 1 mg and 2 mg ESZ treatment groups, respectively. Some

SAEs of accidental injury were also observed in the Chronic Insomnia trials, as described in the review of the original NDA.

Reviewer Labeling Recommendations Regarding Item 2B on the Incidence of Accidental Injury

Sonata® labeling has language under Clinical Trials, Warnings and Precautions regarding various related areas such as psychomotor function, reaction time, use of machinery/driving and use in elderly that in turn influence proneness to accidents and accidental injury that generally appears appropriate for the drug class and for ESZ labeling. The sponsor's proposed labeling

Also refer to conclusions and labeling recommendations regarding related topics (sedative, psychomotor, cognitive and other effects) that in turn influence proneness to accidents and falls under Items 7 and 9 below. Additionally, Item 6 below describes orthostatic and vital sign results in which observed effects could in turn result in dizziness and syncope, and could increase risk of accidents and falls. Yet, results on outliers on orthostatic hypotension were generally not associated with dizziness (in only a few subjects) and none of the outliers had syncope, as described under Item 6, below. Furthermore, no adverse events of syncope were reported in the two elderly and the two longterm non-elderly Chronic Insomnia trials (190-047, -048, -046, -049, respectively).

Clinical Item 3. Unpleasant Taste as a Potential Confounding Variable Influencing Efficacy Results

Approvable Letter Comment

We note a very high (and dose related) incidence of unpleasant taste in the controlled trials, and are concerned that this might have partially unmasked the trial. Please address this concern. For example, you might consider analyzing results separately in the patients who did, or did not, report this adverse event. You may also wish to examine the time course of this event; if the event occurred only early in the course of treatment, it might have had a negligible effect on the outcome later in time. You may also consider the potential effects of unblinding on the various endpoints used in the trials.

The sponsor reanalyzed their efficacy data (for primary, key secondary and other efficacy variables) for studies: 190-026 (transient insomnia trial), 190-046 (6-week Chronic Insomnia trial), 190-047 (one of the two, 2-week, elderly chronic insomnia trials) and 190-049 (6-month DB phase Chronic Insomnia trial). The sponsor did not conduct a reanalysis on Study 190-045 (a 6-way cross-over Chronic insomnia trial) or on the other 2-week elderly chronic insomnia trial (Study 190-048 which was a sleep diary study). The other elderly study that was included in the re-analyses (Study 190-047) used PSG efficacy results, as well as subjective efficacy measures.

Sponsor's Results to Item 3 and Reviewer Comments and Recommendations:
The trials selected for the reanalysis appear to be appropriate and include trials in which dose-dependent effects on unpleasant taste were clearly observed. Cross-over studies are difficult to interpret and the elderly trial selected for the reanalysis was the one that included both subjective and objective efficacy measures, while the other elderly trial only used subjective measures.

The sponsor was able to consistently show significant treatment group effects in the subgroup of subjects with no AE of unpleasant taste and the sample sizes of this subgroup represented the majority of subjects (e.g. for study 190-046 generally over 70 subjects without unpleasant taste AEs in each treatment group, study 190-049 had 394 ESZ subjects and 161 placebo subjects.)

The sponsor conducted an analysis of the timing of an efficacy response relative to the time-point that unpleasant taste was reported, as requested in the Approvable Letter. The results of this analysis are difficult to interpret, since one must assume that the AE resolved shortly after the onset of the AE. However, since this analysis was requested the results are described in the following. Kaplan Meier estimates for the time when the AE was generally reported was approximately 20 days in Study 190-046 with the majority of AEs being reported within the first 2-weeks in this study and in Study 190-049 (although, AEs continued to be reported over several months in this longer term study). Significant treatment group effects on efficacy measures were observed at later time-points in these trials, as previously described in the review of the original NDA. Despite these observations, it is not clear if unpleasant taste resolved or continued once a subject had this event. One would generally anticipate that an unpleasant tasting pill would continue to taste unpleasant, as long as one continues treatment intermittently (e.g. once a night).

Clinical Item 6A-C. Vital Sign and ECG Effects Near Tmax

You have not provided sufficient data on orthostatic vital sign changes. We believe these data are important, and request that you provide this information, adequately assessed and evaluated at appropriate times (e.g., at least at Tmax) after dosing.

Further, you have not provided an adequate presentation of the proportion of patients who meet appropriate outlier (potentially clinically significant) criteria for vital signs and EKG intervals at appropriate times after dosing. Please do so.

6A. Sponsor Response to Item 6A on the Incidence of Outliers on Orthostatic Vital Signs

The sponsor provides the incidence of orthostatic hypotension in studies that collected this data, which were daytime Studies 190-001 and -002, in healthy adults and a daytime study in elderly healthy subjects, Study 190-005. Orthostatic vital signs were obtained at screening, 15, 30 and 60 minutes post-dose, except in Study -005 which did not employ a 60 minute time-point, but instead had a 90 minute time-point at post-dose (in addition to the other time-points). The healthy adult studies had approximately 6 subjects in each treatment group and included dose-levels that ranged from 1 mg to 7.5 mg and a placebo group. The elderly study used dose-levels of 1,2, 3 or 5 mg. Study -001 was a single-dose study and Studies -002 and -005 had a 7-day multiple dose regimen. It is not clear if these studies were parallel group or cross-over studies, although the elderly trial appears to be a parallel group study which had a total of 36 subjects, with 6 subjects in each ESZ group (4 dose-levels) and 12 placebo subjects.

Orthostatic hypotension is defined in these studies as a ≥10 mmHG drop or a ≥20 mmHg drop of systolic blood pressure or diastolic blood pressure, respectively from supine to standing, after a 3 minute period.

Results and Reviewer Comments Regarding Item 6A on Orthostatic Hypotension Outlier Results. *First, it is important to note that the sponsor's definition for orthostatic hypotension did not include an increase in heart rate. The clinical definition of orthostatic hypotension generally includes an increase in heart rate, as well as a decrease in blood pressure. Perhaps, the sponsor's definition would result in an overestimation of the incidence of outliers. Although one cannot be certain. Furthermore, vital sign measures were obtained after a 3 minute period after standing from supine, which in turn could reduce the sensitivity of detecting orthostatic effects.*

Non-Elderly Phase I Studies. *The studies on healthy non-elderly adults failed to reveal a clear or dose-dependent effect on the incidence of orthostatic hypotension events and all subjects were asymptomatic. The following table summarizes the results as provided by the sponsor.*

Table 6A-2. Incidence of Orthostatic Hypotension in Adult Subjects (Studies 190-001 and 190-002)

Day	Study	Eszopiclone 1 mg Subj. n/N (%)	1 mg OH Evt/ Asm	2 mg Subj. n (%)	2 mg OH Evt/ Asm	2.5 mg Subj. n (%)	2.5 mg OH Evt/ Asm	3 mg Subj. n (%)	3 mg OH Evt/ Asm	3.75 mg Subj. n (%)	3.75 mg OH Evt/ Asm	5 mg Subj. n (%)	5 mg OH Evt/ Asm	6 mg Subj. n (%)	6 mg OH Evt/ Asm	7.5 mg Subj. n (%)	7.5 mg OH Evt/ Asm	Placebo Subj. n (%)	Placebo OH Evt/ Asm
Day 1	001	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	--	--	0/10 (0)	0/ 30	0/34 (0)	0/ 102
	002	1/12 (8.3)	1/ 72	--	--	--	--	1/12 (8.3)	1/ 72	--	--	--	--	2/12 (16.7)	2/ 72	--	--	1/12 (8.3)	2/ 72
	001+ 002	1/18 (5.6)	1/ 90	0/6 (0)	0/ 18	0/6 (0)	0/ 18	1/18 (5.6)	1/ 90	0/6 (0)	0/ 18	0/6 (0)	0/ 18	2/12 (16.7)	2/ 72	0/10 (0)	0/ 30	1/46 (2.2)	2/ 174
Day 7	001	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	002	0/12 (0)	0/ 36	--	--	--	--	2/12 (16.7)	2/ 36	--	--	--	--	0/12 (0)	0/ 36	--	--	1/12 (8.3)	1/ 36
	001+ 002	0/12 (0)	0/ 36	--	--	--	--	2/12 (16.7)	2/ 36	--	--	--	--	0/12 (0)	0/ 36	--	--	1/12 (8.3)	1/ 36
Day 1 + Day 7	001	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	0/6 (0)	0/ 18	--	--	0/10 (0)	0/ 30	0/34 (0)	0/ 102
	002	1/12 (8.3)	1/ 108	--	--	--	--	3/12 (25.0)	3/ 108	--	--	--	--	2/12 (16.7)	2/ 108	--	--	1/12 (8.3)	3/ 108
	001+ 002	1/18 (5.6)	1/ 126	0/6 (0)	0/ 18	0/6 (0)	0/ 18	3/18 (16.7)	3/ 126	0/6 (0)	0/ 18	0/6 (0)	0/ 18	2/12 (16.7)	2/ 108	0/10 (0)	0/ 30	1/46 (2.2)	3/ 210

Note: Subj = subject; n/N = subjects with orthostatic hypotensive event (n) relative to total number of randomized subjects in the respective group (N); OH = orthostatic hypotension; Evt = number of post-dosing orthostatic events; Asm = total number of assessments; -- = treatment group or assessment time point not represented in that study.

Note: Percentages are based on number of subjects randomized. Orthostatic hypotension was defined as a decrease of ≥20 mmHg in systolic or ≥10 mmHg in diastolic blood pressure after the subject was standing for at least 3 minutes compared to the blood pressures measured in the supine position. Only post-dose occurrences of PH have been included on this table

Elderly Study 190-005. *In contrast to the above 2 studies on healthy adults, the elderly study (Study -005) shows dose-dependent and time-dependent numerical effects (based on numerical comparisons, statistical comparisons were not conducted) on the incidence of subjects with orthostatic hypotension. Results are shown in the tables below (as provided by the sponsor) and are summarized thereafter.*

Incidence of Orthostatic Hypotension in Elderly Subjects in Study 190-005 (Table 6A-3 in the submission)

Day	Post-dose time	Eszopiclone 1 mg (N=6) Subject n (%)	Eszopiclone 1 mg Ortho event/assess	Eszopiclone 2 mg (N=6) Subject n (%)	Eszopiclone 2 mg Ortho event/assess	Eszopiclone 3 mg (N=6) Subject n (%)	Eszopiclone 3 mg Ortho event/assess	Eszopiclone 5 mg (N=6) Subject n (%)	Eszopiclone 5 mg Ortho event/assess	Placebo (N=12) Subject n (%)	Placebo Ortho event/assess
Day 1	15 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	1 (25.0)	1/4	0 (0.0)	0/12
	30 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	0 (0.0)	0/6	0 (0.0)	0/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	2 (33.3)	2/6	1 (16.7)	1/6	0 (0.0)	0/12
	≤90 min	0 (0.0)	0/18	0 (0.0)	0/18	2 (33.3)	3/18	1 (16.7)	2/16	0 (0.0)	0/36
	8 hrs	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	0 (0.0)	0/6	0 (0.0)	0/12
	All	0 (0.0)	0/24	0 (0.0)	0/24	3 (50.0)	4/24	1 (16.7)	2/22	0 (0.0)	0/48
Day 2	15 min	2 (33.3)	2/6	0 (0.0)	0/6	2 (33.3)	2/6	1 (16.7)	1/6	0 (0.0)	0/12
	30 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	2 (33.3)	2/6	0 (0.0)	0/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	2 (33.3)	2/6	0 (0.0)	0/12
	≤90 min	2 (33.3)	2/18	0 (0.0)	0/18	2 (33.3)	3/18	3 (50.0)	5/18	0 (0.0)	0/36
	8 hrs	0 (0.0)	0/6	0 (0.0)	0/6	2 (33.3)	2/6	1 (16.7)	1/6	0 (0.0)	0/12
	All	2 (33.3)	2/24	0 (0.0)	0/24	2 (33.3)	5/24	3 (50.0)	6/24	0 (0.0)	0/48
Day 3	15 min	0 (0.0)	0/6	0 (0.0)	0/6	2 (33.3)	2/6	2 (33.3)	2/6	0 (0.0)	0/12
	30 min	0 (0.0)	0/6	1 (16.7)	1/6	1 (16.7)	1/6	1 (16.7)	1/6	1 (8.3)	1/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	≤90 min	0 (0.0)	0/18	1 (16.7)	1/18	2 (33.3)	3/18	2 (33.3)	3/18	1 (8.3)	1/36
	8 hrs	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	1 (8.3)	1/12
	All	0 (0.0)	0/24	1 (16.7)	1/24	2 (33.3)	3/24	2 (33.3)	4/24	2 (16.7)	2/48
Day 4	15 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	30 min	0 (0.0)	0/6	0 (0.0)	0/6	2 (33.3)	2/6	0 (0.0)	0/6	1 (8.3)	1/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	≤90 min	0 (0.0)	0/18	0 (0.0)	0/18	2 (33.3)	2/18	0 (0.0)	0/18	1 (8.3)	1/36
	8 hrs	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	All	0 (0.0)	0/24	0 (0.0)	0/24	2 (33.3)	2/24	0 (0.0)	0/24	1 (8.3)	1/48

Incidence of Orthostatic Hypotension in Elderly Subjects in Study 190-005, continued (Table 6A-3 in the submission)

Day	Post-dose time	Eszopiclone 1 mg (N=6)		Eszopiclone 2 mg (N=6)		Eszopiclone 3 mg (N=6)		Eszopiclone 5 mg (N=6)		Placebo (N=12)	
		Subject n (%)	Ortho event/assess	Subject n (%)	Ortho event/assess	Subject n (%)	Ortho event/assess	Subject n (%)	Ortho event/assess	Subject n (%)	Ortho event/assess
Day 5	15 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	0 (0.0)	0/6	1 (8.3)	1/12
	30 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	2 (33.3)	2/6	1 (8.3)	1/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	2 (33.3)	2/6	1 (8.3)	1/12
	≤90 min	0 (0.0)	0/18	0 (0.0)	0/18	2 (33.3)	3/18	3 (50.0)	4/18	3 (25.0)	3/36
	8 hrs	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	All	0 (0.0)	0/24	0 (0.0)	0/24	2 (33.3)	3/24	3 (50.0)	4/24	3 (25.0)	3/48
Day 6	15 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	30 min	0 (0.0)	0/6	0 (0.0)	0/6	2 (33.3)	2/6	0 (0.0)	0/6	1 (8.3)	1/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	≤90 min	0 (0.0)	0/18	0 (0.0)	0/18	2 (33.3)	2/18	0 (0.0)	0/18	1 (8.3)	1/36
	8 hrs	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	All	0 (0.0)	0/24	0 (0.0)	0/24	2 (33.3)	2/24	0 (0.0)	0/24	1 (8.3)	1/48
Day 7	15 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	0 (0.0)	0/6	0 (0.0)	0/12
	30 min	0 (0.0)	0/6	0 (0.0)	0/6	1 (16.7)	1/6	3 (50.0)	3/6	0 (0.0)	0/12
	90 min	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/5	0 (0.0)	0/12
	≤90 min	0 (0.0)	0/18	0 (0.0)	0/18	2 (33.3)	2/18	3 (50.0)	3/17	0 (0.0)	0/36
	8 hrs	1 (16.7)	1/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/6	0 (0.0)	0/12
	All	1 (16.7)	1/24	0 (0.0)	0/24	2 (33.3)	2/24	3 (50.0)	3/23	0 (0.0)	0/48

While results at the lower dose-levels (1 and 2 mg treatment groups) are unremarkable (no events occurred on most time-points on most days), the 3 mg and 5 mg groups showed an incidence of up to 33% and 50%, respectively for a given time-point on a given treatment day. There also is a numerically greater incidence at the 30, 90 and ≥90 min time-point in the 3 mg and 5 mg group compared to the incidence at 8 hours which was generally 0-17% (17% corresponds to 1/6 subjects in a given treatment group, with one exception of 33%, observed at only one of the 5 time-points for the given day, on only one of the 7 days at this single time-point, and in only 1 of the 5 treatment groups). This time-dependent pattern was most apparent after the first and second daily doses (Days 1 and 2). While the events appeared less clustered near Tmax on subsequent days of treatment, the magnitude of the maximum effect generally remained the same across days of treatment, suggesting that tolerance to this effect did not appear to develop over the 7-day treatment period.

Only one event of orthostatic hypotension in the elderly subjects was associated with symptoms, which was dizziness (Subject 405). Multiple episodes of orthostatic hypotension were observed in subjects at the two highest dose-levels (3 mg/day and 5 mg/day observed in subjects 24, 29, 4042 and 405). Only one of these subjects had symptoms of approximately 15 minutes of dizziness on Day 7 of treatment that resolved without treatment.

Adverse Events of Syncope, Dizziness and Falls in Chronic Insomnia Trials. *The sponsor also provides the incidence of dizziness, syncope and falls in the following Chronic Insomnia trials: a non-elderly 6-week study 190-046 (DB placebo or 3 mg/day ESZ), a non-elderly longterm Study 190-049 (6 month DB placebo or 3 mg/day ESZ) and for the two 2-week elderly trials, Studies 190-047 and 190-048 (placebo or 2 mg/day ESZ and fewer subjects given 1 mg/day). This information was previously provided and described in the review of the original NDA. Also refer to Item 2B, above, regarding falls and accidental injuries.*

Most notable among the results of the incidence of these specific AEs in these four Chronic Insomnia trials (non-elderly and elderly), is that no AEs of syncope were reported in these Chronic Insomnia trials.

Treatment group effects compared to placebo on the incidence of dizziness (an effect is defined as an incidence in a ESZ group of 2x's greater than placebo) were observed at the 2 mg/day ESZ dose-level in the 2-week elderly study (6% compared to 2% in the placebo group), and at the 3 mg/day ESZ dose-level in non-elderly studies (Study 190-046; 7%, 4%, respectively and 5% in the 1 mg/day group and Study 190-049; 10%, 3% respectively, no other ESZ dose-levels were employed). Given that this effect was at a lower dose-level in elderly than non-elderly and that the elderly trials were shorter than the non-elderly trials (possibly greater group differences would be revealed with a longer treatment period), the elderly show greater effects of ESZ on the incidence of dizziness. These observations should be described in labeling, with emphasis on greater effects in elderly at lower dose-levels. The physiological drug-mediated mechanism underlying events of dizziness were not examined and remains unclear. As previously described under Item 2B, there were few falls (only 3/215 elderly subjects in the 2 mg/day group and 5/593 non-elderly subjects in the 3 mg ESZ group in the longer term study, Study 190-049, that also had 1/195 placebo subjects who had this adverse event). A slightly higher incidence of accidental injuries were observed, as previously described (not clear if these injuries were associated with dizziness or other adverse events). Also there were no cases of syncope.

Reviewer Labeling Recommendations Regarding Item 6A on Orthostatic Hypotension Outlier Results. *The recommended dose for elderly patients in proposed labeling is 1 mg which may be increased to 2 mg.*

If the NDA is approved at the Agency level, it is recommended that approved labeling describe results of elderly on orthostatic hypotension (observed at higher dose-levels), emphasizing that these results were not observed in non-elderly subjects at comparable dose-levels, as well as at higher dose levels.

Since there were no associated symptoms except for transient insomnia in one subject, and the 1 and 2 mg dose-levels revealed unremarkable results, the 1 and 2 mg dose-levels for elderly are considered to be adequately safe (for short term treatment of Chronic Insomnia) with respect to orthostatic hypotension (as long as a subject is not at risk or has abnormal drug metabolism).

Item 6B. Results on the Incidence of Outliers on Vital Sign Measures

The sponsor provided the incidence of vital sign outliers using specified cut-off criteria for 11 day-time (1-7 day) Phase I studies (Studies -001, -002, -005, -010, -011, -012, -015, -018, -019, -020 and -023) at the following time-points post-dose (data pooled): 30, 60, 90, 120 minutes, 30-120 minutes (pooled data from time-points within this range), 0-6 hours (pooled data within this range of time-points). The dose-levels employed in these trials, combined, included 1 mg, 2 mg, 2.5 mg, 3 mg and ≥3.5 mg and placebo. The 1 mg and 2.5 mg dose-levels only had 24 and 6 subjects, respectively. The other dose-levels had 52 to 124 subjects at a given dose-level (some trials may be cross-over studies).

Most of the studies were single-dose studies. Similar information was provided in end-of-text tables or appendices for an elderly Phase I study, Study 190-005 that had assessments near Tmax.

Since the greatest treatment group differences were observed with systolic blood pressure changes (see reviewer comments below), the results on this parameter are provided below (as provided by the sponsor).

Table 6B-9. Frequency of Potentially Clinically Significant (PCS) Systolic Blood Pressure by Treatment and Post-Dose Time Point in Daytime, 1- to 7-Day Studies in Healthy Volunteers

Parameter	Post-Dose Time Point	PCS Criteria	Placebo (N=124)	ESZ 1 mg (N=24)	ESZ 2 mg (N=52)	ESZ 2.5 mg (N=6)	ESZ 3 mg (N=123)	ESZ ≥3.5 mg (N=91)
Systolic Blood Pressure (mmHg)	30 min	PCS Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
		PCS High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	60 min	PCS Low	0 (0.0)	1 (4.2)	2 (3.8)	0 (0.0)	5 (4.1)	1 (1.1)
		PCS High	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	90 min	PCS Low	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (3.3)
		PCS High	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	120 min	PCS Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		PCS High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	30-120 min	PCS Low	0 (0.0)	1 (4.2)	2 (3.8)	1 (16.7)	6 (4.9)	3 (3.3)
		PCS High	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	0-6 hrs	PCS Low	0 (0.0)	1 (4.2)	2 (3.8)	1 (16.7)	7 (5.7)	5 (5.5)
		PCS High	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: PCS=potentially clinically significant; ESZ=eszopiclone. Data from Studies 190-001, 190-002, 190-005, 190-010, 190-011, 190-012, 190-015, 190-018, 190-019, 190-020, and 190-023 were included. The assignment of a PCS category for a subject was based upon all post-baseline data. Each subject contributed once to each administered treatment. A vital sign was PCS Low if a subject had a value below a defined lower limit and had a decrease from baseline greater than a defined limit. A vital sign was PCS High if a subject had a value above a defined upper limit and had an increase greater than a defined limit.

Note: For systolic blood pressure, PCS Low: <90 mmHg and ≥20 mmHg decrease from baseline; PCS High: >180 mmHg and ≥20 mmHg increase from baseline.

Reference: TOC Table 6.2.1

Results of the elderly trial, Study 190-005 are also summarized with reviewer comments below.

Results and Reviewer Comments Regarding Item 6B on Vital Sign Outliers. *Outlier criteria are similar to those generally used in clinical trials. The outlier criteria used for these analyses are adequate.*

The sponsor included data from an elderly trial, Study 190-005 in the above summary table showing results on incidence of outliers in healthy volunteer, Phase I trials. Yet, the sample size of elderly subjects was small. Given the caveat that the results were of elderly and non-elderly subjects combined, the following observations are noted upon further examination of the sponsor's results.

In summary, the results show a small dose-dependent numerical effect (no statistical comparisons were made) on the incidence of outliers on low systolic and diastolic blood pressure[1] at time-points near the anticipated Tmax. 4% of 2mg ESZ subjects had low systolic blood pressure and 3% had low diastolic blood pressure (at the recommended starting dose of 2 mg in proposed labeling) compared to 0% in placebo treated subjects. These results may be somewhat diluted by including data from an elderly study (190-005)

[1] Decrease systolic blood pressure was defined as a systolic blood pressure of <90 mmHg that had also decreased from baseline by at least 20 mmHg. Decreased diastolic blood pressure was defined as diastolic blood pressure of <50 mmHg that also decreased from baseline by at least 15 mmHg.

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in which this elderly trial did not reveal any remarkable treatment group effects on vital sign outliers. However, there were only 6 subjects in each active treatment group in this study and 12 placebo treated subjects.

An even smaller numerical effect was observed for low temperature (1% at a given dose-level compared to 0% after placebo).

Results in a small study of elderly subjects (Study 190-005) generally showed similar results, except that outliers were generally only observed at a ≥3.5 mg dose-level (17-33%, representing only 1 or 2 subjects out a total of 6 subjects), while dose-levels of 2 mg and less and placebo treatment generally showed an incidence of 0% (N=6/ESZ dose-level and N=12 in the placebo treatment condition).

It is not clear if any of the above outliers were associated with adverse events. However, the sponsor previously noted that the Chronic Insomnia trials of elderly subjects (190-047 and190-048) and the 6-week and longer term non-elderly Chronic Insomnia trials (190-046 and 190-049) had no AEs of syncope.

<u>The following paragraphs described the results in more detail.</u>
The greatest incidence of outliers was observed for outliers on low systolic blood pressure which showed numerically greater incidence at each ESZ dose-level (generally 4-6%/dose-level) compared to placebo (0%) at 30-120 minutes post-dose (pooling time-points within this period). The 2.5 mg dose-level showed the highest incidence of 17% but this dose-level only had 6 subjects. Despite these observations, the incidence at the 2 mg ESZ dose-level (the recommended dose-level in proposed labeling for non-elderly adults) was 4% which represents only 2 out of 52 subjects.

Similar results were observed with outliers on low diastolic blood pressure, but the maximum observed incidence was only 3% (at 30-120 minutes and at 0-6 hours) in the 3 mg ESZ group (2% in the ≥3.5 mg group at 30-120 minutes and generally 0% at lower dose-levels and placebo).

The incidence of high systolic blood pressure outliers and outliers on heart rate was generally 0% at any given time-point, at any given dose-level.

One subject at each of the higher dose-levels of 2 mg, 3mg and 3.5 mg (1-2%) was an outlier on low temperature (at 60 minutes post-dose), compared to 0 subjects at lower dose-levels and compared to placebo. These results on low temperature are contrasted to results of outliers on high temperature, in which no subjects met outlier criteria for high temperature at any dose-level and at any time-point.

The incidence of outliers on vital signs in elderly subjects was provided using data from a 7-day trial, Study 190-005 (results were provided for individual and combined time points of 30-120 minutes in a SD study using 1, 2, 3, and over 3.5 mg dose-levels, with 6 subjects per group and 12 subjects receiving placebo). These results were unremarkable, except at the ≥3.5 mg dose-level. This high dose-level showed an

incidence of 17-33% (represents 1 or 2 subjects out of 6 total subjects) with low systolic blood pressure near the anticipated Tmax (compared to 0% in all other groups). A similar incidence of subjects was observed at this high dose level for outliers on low body temperature at time-points near the anticipated Tmax (compared to 0% in other groups).

Additional Reviewer Comments Regarding Statistical Descriptive Vital Sign Results (provided in the 120-Day Safety Update Report).

Similar results were observed on the mean change of systolic and diastolic blood pressure described in section VIIK of the Clinical Review of the original NDA. Results of orthostatic measures could not be found in the original NDA and 120-day update submission. See Item 6A above for orthostatic measure results provided in the current submission.

As previously described, at least trends for a mean decrease in systolic and diastolic blood pressures that was greater in ESZ groups compared to placebo and was dose-dependent (greater mean decrease across increasing dose-levels) at 30-120 minutes post-dose in the short term day-time Phase I studies (data pooled). These observations are based on numerical comparisons (statistical comparisons were not conducted). The magnitude of the effect was no greater than a 6 mmHg mean decrease in systolic blood pressure at the 2 mg, 3 mg and 3.5 mg dose-levels compared to a 1 mmHg increase with placebo treatment. A mean increase in heart-rate was also described in the review of the original NDA.

The above observations appear to be partly reproduceable in Chronic insomnia trials, despite that vital signs were obtained in the daytime that do not reflect effects near Tmax. The incidence of outliers on low systolic, low diastolic blood pressure and increased heart rate showed at least numerical trends for effects with ESZ treatment compared to placebo in the DB phase of the long-term chronic insomnia study (Study 190-049). An even greater incidence of outliers on these parameters was observed with OL treatment, although it is difficult to interpret OL findings, since a control group was not employed. Refer to the clinical review of the original NDA under Section VIIIK4 for details on these observations.

Reanalyses of Vital Sign Data provided in a 9/30/04 Submission Upon Request (separating elderly-trial-data from non-elderly-trial-data)

The sponsor combined elderly with non-elderly trial data in the above results of healthy volunteer Phase I trials and in previous submission. Therefore, upon request, the sponsor provided vital sign results for non-elderly trials and elderly trials, separately (results were from Day 1-7 day-time studies that had assessments conducted near Tmax). The results provided by the sponsor in the recent 9/30/04 submission are summarized below regarding a reanalysis of data from non-elderly subjects. Results of elderly subjects, as provided in the 9/30/04 submission are summarized thereafter.

Tables in this subsection below and in the subsection on elderly subject provided thereafter, show results from selected time-points. These time-points were selected since they include time-points near the anticipated Tmax and were time-points in which

numerical treatment group differences (between each ESZ group and placebo) appeared to be most robust (based on numerical comparisons).

Note the small sample size of the 1 mg and 2.5 mg groups in the summary table below, which only had 18 and 6 subjects, respectively. Results for these groups may be difficult to interpret. When examining results of the larger treatment groups, a small signal for decreased systolic and diastolic blood pressure is observed (based on numerical comparisons).

Tables A and B: Vital Sign Results in the Non-elderly of Day 1-7 trials in Non-Elderly Trials Only (excludes data from elderly study, 190-005) in which Assessments were Conducted Near Tmax (provided End-of-Text Tables 1.1.1-1.2.2 in the "Comment 1" section of the 9/30/04 submission)

Table A: Incidence of Outliers on Selected Post-Dose Timepoints

Parameter	Post-Dose Time Point	PCS Criteria	Placebo (N=112)	Eszopiclone 1 mg (N=18)	2 mg (N=46)	2.5 mg (N=6)	3 mg (N=117)	>=3.5 mg (N=85)
Systolic BP (mmHg)	30-120 minutes	PCS Low	0 (0.0 %)	1 (5.6 %)	2 (4.3 %)	1 (16.7%)	6 (5.1 %)	1 (1.2 %)
		PCS High	1 (0.9 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

Parameter	Post-Dose Time Point	PCS Criteria	Placebo (N=112)	Eszopiclone 1 mg (N=18)	2 mg (N=46)	2.5 mg (N=6)	3 mg (N=117)	>=3.5 mg (N=85)
Diastolic BP (mmHg)	30-120 minutes	PCS Low	1 (0.9 %)	1 (5.6 %)	1 (2.2 %)	0 (0.0 %)	3 (2.6 %)	2 (2.4 %)
		PCS High	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

Parameter	Post-Dose Time Point	PCS Criteria	Placebo (N=112)	Eszopiclone 1 mg (N=18)	2 mg (N=46)	2.5 mg (N=6)	3 mg (N=117)	>=3.5 mg (N=85)
Heart Rate (bpm)	30-120 minutes	PCS Low	1 (0.9 %)	0 (0.0 %)	1 (2.2 %)	0 (0.0 %)	0 (0.0 %)	1 (1.2 %)
		PCS High	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (1.2 %)

Table B: Change from Baseline to Selected Post-Dose Timepoints

Parameter (units)	Measurement[2]	Time Point	Statistic	Placebo (N=112)	Eszopiclone 1 mg (N=18)	2 mg (N=46)	2.5 mg (N=6)	3 mg (N=117)	>=3.5 mg (N=85)	All Active (N=259)
Systolic BP (mean change from baseline, mmHg)										
		30-120 Mins	N	112	18	46	6	117	85	259
			MEAN	1.8	-2.4	-5.8	-1.7	-5.3	-2.5	-4.1
			SD	7.85	4.21	8.99	8.66	8.40	7.76	7.99
			MINIMUM	-15.0	-8.3	-35.5	-14.3	-33.0	-25.2	-35.5
			MEDIAN	2.0	-2.3	-5.3	-2.8	-5.0	-1.8	-3.4
			MAXIMUM	26.0	4.3	14.0	8.5	19.5	18.0	19.5
Diastolic BP (mean change from baseline, mmHg)										
		30-120 Mins	N	112	18	46	6	117	85	259
			MEAN	0.2	-3.2	-1.6	1.1	-2.8	-1.0	-2.2
			SD	5.03	5.28	6.35	4.76	5.94	6.14	5.73
			MINIMUM	-14.0	-15.5	-22.5	-5.5	-17.5	-16.0	-22.5
			MEDIAN	0.0	-2.8	-1.3	0.5	-2.5	0.7	-1.8
			MAXIMUM	13.0	8.0	15.0	8.8	15.0	13.0	15.0
Heart Rate (mean change from baseline, bpm)										
		30-120 Mins	N	112	18	46	6	117	85	259
			MEAN	0.0	1.2	-0.4	4.4	1.3	3.6	2.1
			SD	6.64	5.16	7.07	7.00	7.17	9.00	7.34
			MINIMUM	-18.0	-9.0	-38.5	-4.0	-18.0	-36.0	-38.5
			MEDIAN	0.0	0.5	0.3	4.5	1.0	4.0	1.5
			MAXIMUM	23.0	10.7	12.5	11.8	24.8	22.0	24.8

The above results shows a decreased systolic and diastolic BP in the eszopiclone groups compared to placebo (based in numerical comparisons). The results on the incidence of outliers were similar for decreased systolic and diastolic BP (heart rate outlier results

were inconsistent). The magnitude of the mean or median change of each parameter is generally, small.

Results on temperature and respiratory rate (incidence of outliers and descriptive statistical results) were unremarkable in the non-elderly subjects.

Vital Sign Results of Assessments Conducted Near Tmax in the Elderly Study 190-005 Provided Upon Request (submitted on 9/30/04)

The sponsor provided outlier results in the current 6/14/04 submission for the elderly trial, Study 190-005 which was the only elderly trial with vital sign assessments near Tmax. These results were described in a previous section on results provided in the current, 6/14/04 submission.

Upon request, the sponsor provided descriptive statistical results on vital sign parameters for this elderly trial in a recent 9/30/04 submission. The following table shows results of selected time-points (results were provided in End-of-Text tables in the 9/30/04 submission). These time-points were selected since they were near the anticipated Tmax and other time-points and group differences (between ESZ and placebo) were generally more robust at theses time-points (based on numerical comparisons).

Descriptive Statistical Results of Change from Baseline to Selected Post-Dose Timepoints on Systolic Blood Pressure in the Elderly Study 190-005 (results are taken from the sponsor's summary table in the9/30/04 submission).

					Eszopiclone				
Parameter (units)	Measurement[2]	Time Point	Statistic	Placebo (N=12)	1 mg (N=6)	2 mg (N=6)	3 mg (N=6)	>=3.5 mg (N=6)	All Active (N=24)
		30 120 Mins	N	12	6	6	6	6	24
			MEAN	-6.8	1.4	-9.8	-16.9	-10.9	-9.0
			SD	9.41	7.07	6.05	9.56	11.40	10.59
			MINIMUM	-25.1	-10.2	18.9	-29.9	-28.7	-29.9
			MEDIAN	6.6	2.6	-10.0	-18.8	-9.9	-9.8
			MAXIMUM	6.2	10.0	-2.6	-2.3	6.6	10.0
		90 Mins Postdose	N	12	6	6	6	6	24
			MEAN	-8.6	0.8	-11.5	-20.3	-11.6	-10.7
			SD	9.82	6.91	5.33	9.24	11.14	11.01

Similar results were observed for diastolic blood pressure at similar time-points (on pages 116-117 in Table 1.1.2 of the clistat\clinsum.pdf file of the 9/30/04 submission). Numerical trends for dose-dependent numerical increase in heart rate appear to be most notable at 90 minutes post-dose (as shown in the sponsor's Table 1.1.2). While dose levels of 3 mg or below were generally similar to placebo, the ≥3.5 mg group showed a mean and median increase of 7 and 9, respectively in diastolic blood pressure compared to increase of 1 and 1, respectively in the placebo group (in units of mmHg).

Results on the incidence of outliers in the elderly trial were previously described, since they were already provided in the current 6/14/04 submission.

Reviewer Conclusions Regarding Vital Sign Results

Eszopiclone is adequately safe with respect vital sign results (as above) for the dose-levels recommended for treatment in non-elderly and elderly subjects.

While vital sign effects appear to exist the magnitude of the effects appear to be small. As previously described, effects appear to be in part reproduceable in Chronic Insomnia trials. Yet, SAEs and ADOs reported in night-time Chronic Insomnia trials did not suggest a cardiovascular related signal (refer to the clinical review of the original NDA for details).

Reviewer Labeling Recommendations Regarding Item 6B on Vital Sign Results
If the NDA is ultimately approved at the Agency level then it is recommended that positive findings revealed in the above re-analyses be described in the Adverse Reaction section of labeling.

Since the Phase I trials reflect effects near Tmax in the daytime and treatment will be given at night time, diurnal effects need to also be considered and noted in labeling (i.e. that effects could be greater at night-time). As previously described, some findings appear to be reproduceable in the Chronic Insomnia trials and should be noted in labeling. The vital sign assessments in the Chronic Insomnia trials were not conducted near Tmax (when the subject would be likely to be asleep). Therefore, it is important to note in labeling that diurnal effects of ESZ on vital signs was not evaluated and that potential effects may be enhanced during sleep or during specific sleep stages.

Item 6C. Results on the Incidence of ECG Outliers
The sponsor provided the incidence of outliers on venticular rate, QT raw interval, QTcF and B intervals for three day-time Phase I studies (Studies 190-002, -005 and -011) data pooled) at 90 minutes post-dose.

Reviewer Comments Regarding ECG Results in Response to Item 6C
The sponsor used adequate outlier criteria and the results were unremarkable for all dose-levels (placebo compared to 1 mg, 2 mg, 3 mg and ≥3.5 mg with approximately 20-50 subjects at each dose-level in which some trials may be cross-over studies).

The sponsor did not provide ECG results for elderly subjects (elderly subjects of 190-005 were pooled with the other Phase I ECG data that was analyzed). However, no subjects had a QT interval (raw) of 500 msec or greater in the trials.

The results on ECG do not reveal any findings to change the safety profile of the study drug, that a previously described in the review of the original NDA, in that ECG findings were unremarkable.

Review of 9/30/04 submission of ECG Results of elderly and non-elderly data analyzed separately.
The sponsor provided ECG results in the current submission and in a previous 120-Safety Update report submission pooling data from non-elderly trials with data from an

elderly trial, Study 190-005. Therefore, upon request the sponsor reanalyzed ECG data for non-elderly subjects only and the results were provided in a 9/30/04 submission.

The ECG results provided in the recent 9/30/04 submission did no reveal any remarkable findings for ECG assessment parameters in the non-elderly Phase I trials (the incidence of outliers and descriptive statistical results of 90 minutes post-dose assessments in day time phase I trials were provided).

Also upon request the sponsor provided ECG results for the elderly trial (data separated from non-elderly Phase I data). These results were those of 90 minute post-dose assessments and were unremarkable (the incidence of outliers and descriptive statistical results).

Reviewer Labeling Recommendations Regarding ECG Results in Response to Item 6C
The following are comments and recommendations if the NDA is ultimately approved at the Agency level. ECG assessments fail to show any remarkable findings. Therefore, ECG results provided by the sponsor do not change the overall safety profile of the drug or proposed labeling with respect to ECG related safety.

III. Clinical Labeling Items in the Approvable Letter (Items 7 and 8) and Itemized Bracketed Comments in Clinical Sections in Labeling Attached to the Approvable Letter (Item 9, A-G)

Clinical Labeling Item 7, a and b. Effects on Psychomotor, Memory and Other Cognitive Effects

Approvable Comment 7a and b.

In labeling you suggest that there is little reason for concern about next day psychomotor impairment or memory problems — after zopiclone is taken, but it was not clear on what objective time-course data this reassurance was based and further explanation is needed. This explanation should describe studies that objectively explored the effects on cognition and psychomotor function at relevant time points after study drug was taken. These descriptions should focus on what functions were measured and whether or not a difference in performance was detected. You should comment on objective measures of memory impairment and sedative/psychomotor effects. Reassuring statements about the lack of effect on psychomotor function and cognition based on spontaneous reports or subjective measures alone are of little help in determining when or if impairment is no longer present.

You should also note that in the presence of a measured impairment on the DSST and in the absence of formal studies of driving ability one can not make any conclusions on how the next day residual effect may influence a complicated function such as driving. Please also note that an objectively measured decrement in functioning together with a reported feeling of being rested and alert (as you suggest is the case) is not reassuring from the standpoint of driving safety, but is cause for concern.

Sponsor's Response to Item 7a and b Psychomotor and Cognitive Effects. The sponsor refers to their response to Item 9A regarding drug effects on these safety parameters. They also acknowledge the "discussion that occurred at the End of Review Conference concerning interactions between the National Transportation Safety Board and the FDA regarding labeling for sleep hypnotics with respect to driving." They aknowldege that labeling may be revised in the future, following this "inter-agency activity."

The sponsor includes standard drug class language in the Warning section regarding the use of machinery and driving.

Clinical Labeling Item 8 (a-b). Withdrawal Effects

Approvable Letter Comment 8 a-b

Please explore the effects of eszopiclone discontinuation and any potential loss of therapeutic effect compared to placebo in the 6-month datasets. Ideally this type of comparison is made in patients who, after taking drug for 6-months, are re-randomized to take either placebo or continue on drug. Since, to our knowledge, this was not done in your development program a comparison of the loss of treatment effect of eszopiclone treated patients when switched to placebo versus placebo patients who continued on placebo during the treatment withdrawal phase of the study would be acceptable.

We note in your draft labeling that you describe the effects of zopiclone withdrawal on the incidence of rebound insomnia. Rebound insomnia is defined as insomnia that is worse than that experienced at baseline. However, there are often measurable losses of effect that are significantly different from placebo that do not reach the level of "rebound". In addition to an analysis of classical rebound, we are also interested in an analysis of this latter phenomenon. Results of this type of exploration should be discussed under the heading of Withdrawal Emergent Anxiety and Insomnia:

Sponsor's Response to Item 8 Regarding Withdrawal Effects

The following are responses and reviewer comments/recommendations (the latter italicized) for each subtopic of the sponsor's response to Item 8. Italicized reviewer comments and recommendations follow each response for each subtopic under Item 8, unless otherwise specified.

Sponsor's Response Regarding Subheadings in Labeling on Withdrawal Effects (Item 8).

The sponsor proposes two subheadings under "Studies Pertinent to Safety Concerns for ...Drugs" that pertain to withdrawal effects, as follows: "Withdrawal Emergent Anxiety and Insomnia"

Reviewer Comments and Labeling Recommndations regarding Subheadings in Proposed Labeling on Withdrawal Effects (Item 8). *The two subheading titles are*

reasonable and are — *However, it recommended that these subheadings be slightly modified to more closely correspond to the content of each subsection.*

Recommendations for exact wording of subheading titles and text under these subsections in labeling are provided later in this review.

Sponsor's Results of Study 190-049 in Describing Withdrawal Effects in Proposed Labeling (Item 8). The "Withdrawal Emergent Anxiety and Insomnia" subsection in proposed labeling includes a description of results of Study 190-049. The results in proposed labeling are described in the clinstat\clinsum.pdf under "Comment 8A of the current submission.

Reviewer Comments and Labeling Recommendations on Describing "Withdrawal Effects" of Study 190-049 in Proposed Labeling (Item 8) *Refer to the Clinical Review of the original NDA for a description of study 190-049 and study results. The study was not adequately designed for examining withdrawal effects, nor did it involve a less optimal study design specified in the Approvable action letter (i.e. subjects treated with eszopiclone in Study 190-049 were not switched to placebo and monitored for withdrawal effects).* —

Sponsor's Results of Study 190-046 Regarding Withdrawal Effects (Item 8). Study 190-046 is also described in proposed labeling under the "Withdrawal Emergent Anxiety..." subsection in proposed labeling and results are described in more detail in the current response submission. Refer to Section VIC of the Clinical Review of the original NDA for a description of this study and study results. The following provides a brief summary of the study design. This 6-week double-blind, placebo controlled, fixed-dose trial of outpatients with Chronic Insomnia included a single-blind placebo 2-day washout phase after receiving 44 days of double-blind placebo or eszopiclone. During the washout (or withdrawal phase) subjects received single-blind placebo each night for 2 nights (Nights 45 and 46) and were monitored during this phase including day-time assessments conducted on the next day after placebo (Days 45 and 46). The sponsor proposes the following in labeling regarding the description of this study under the section of labeling on withdrawal effects:

> Rebound insomnia following discontinuation of — relative to baseline was —

Reviewer Comments and Labeling Recommendations in Describing Results of Study 190-046 in Proposed Labeling *. This reviewer disagrees with statements in proposed labeling and the sponsor's overall conclusions.*

Reviewer's Labeling Recommendations in Describing Withdrawal-Emergent Insomnia (Item 8)

Given, the above recommendations relevant to the "Withdrawal-Emergent..." section of labeling, it is also recommended that the titles of these be modified to more closely resemble the content of each subsection. Consequently, it recommended that the "Withdrawal-Emergent Anxiety and Insomnia" title be changed to the following title in labeling (in italics, underlined and in blue font):

It is recommended that the above proposed paragraphs in this subsection of labeling be replaced by the following text (italicized, underlined and in blue font):

Additional Reviewer Comments and Labeling Recommendations regarding Withdrawal Effects in the Elderly in Proposed Labeling (Item 8)

The Clinical Review of the original NDA submission describes withdrawal AEs observed in the one elderly Chronic Insomnia trial (Study 190-047) that examined potential withdrawal effects (monitored subjects during a 2-day non-placebo controlled washout period following the 2-week treatment phase). These observations cannot be found in

proposed labeling and should be described in relevant sections. It is recommended that these findings be included in appropriate sections of labeling.

**Sponsor's Response to Item 8 regarding the "
' subsection under ' in
Labeling**

The sponsor proposes the following language for the following subsection of labeling.

Clinical Item 9, A-G. Itemized Comments in Clinical Sections of Labeling

The sponsor itemized bracketed comments in proposed labeling of the Approvable letter and responded to each itemized bracketed comment (referred to as Clinical labeling items). Each of these items is provided below with a copy of the corresponding bracketed labeling comments (as they appear in the approvable labeling and in the sponsor's submission) to which the sponsor provided a response. A description of the sponsor response for the given item is then provided, followed by reviewer comments and recommendations (reviewer comments and recommends appear in unbracketed italicized font).

Clinical Labeling Item 9A. This section refers to subsections of the section on "Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs," that are not previously described (under Item 8 above)

[This section should be devoted to the description of studies that objectively explored the effects on cognition that patients experienced the day after eszopiclone was used. Please re-write it to cover this topic. These descriptions should focus on what functions were measured and whether or not a difference in performance was detected. You should comment on the following concerns: Memory Impairment; Sedative/Psychomotor Effects; Withdrawal Emergent Anxiety and Insomnia; and Other Withdrawal Emergent Phenomena. Reassuring statements of lack of effect based on spontaneous reports or subjective measures alone should not be made when objective measures are absent.

You should also note that in the presence of a measured impairment on the DSST and in the absence of formal studies of driving ability one can not make any conclusions on how the next day residual effect may influence a complicated function such as driving. Please also note that an objectively measured decrement in functioning along with a reported feeling of being rested and alert (as you suggest is the case) is alarming as opposed to reassuring from the standpoint of driving safety.]

[We note that Sleep EEG findings during drug treatment as compared to placebo have been correlated with patients' subjective feelings of being rested the next day and REM rebound. These measures are not recognized as surrogate markers of efficacy or safety for the purpose of labeling].

Response to 9A on "Next Day" Effects.

Subtopics under Item 9A are addressed as subsections below. The sponsor's response and reviewer comments and recommendations are provided for each subtopic.

Item 9A Regarding Subheadings under "Studies Pertinent to Safety..." in Proposed Labeling The sponsor proposes to have subsections in labeling under the above heading of "Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs." The first subheading is " nstead of other subheadings of Memory Impairment and Sedative/Psychomotor Effects) followed by "Withdrawal-Emergent Anxiety and Insomnia," which in turn, is followed by Item 9A is regarding proposed labeling under " "Withdrawal Emergent Anxiety and Insomnia" section of proposed labeling corresponds

to Item 8 (above) and the last section of "Other ...Effects" was also addressed under Item 8.

Reviever Comment Regarding Proposed Labeling subsections headings under "Studies Pertinent to Safety Concerns for..." *It is recommended that the subsection headings be changed and parallel more closely the standard headings used for approved drugs in this drug class (refer to Sonata® labeling). Recommendations for these subheadings are provided in blue font later with other labeling recommendations relevant to each subheading and/or subtopic (as specified).*

Item 9A Regarding a Description of Results on Memory Impairment and Sedative/Psychomotor Effects. In response the sponsor has a section on "Next I [illegible] ,' instead of sections of "Memory [illegible] ' and "Sedative/Psychomotor Effects," (refer to Sonota® labeling for guidance).

Results on memory, cognitive and psychomotor tests based on results of Studies 190-024 and -025 are described in proposed labeling under the ' [illegible] subheading. Results of effects on DSST measures are also described in this subsection of proposed labeling. The submission also provides the results of these studies (under Item 9) in the clinstat\clinsum.pdf. Refer to the Clinical Review of the original NDA for a description of these studies and study results.

Although, this subsection of proposed labeling is called by the sponsor, ' [illegible] the sponsor also describes effects on DSST near Tmax in a daytime Phase I study (Study 190-001) in healthy volunteers.

The results that the sponsor shows for Study 190-001 (in the clinstat\clinsum.pdf of the current submission) do not include results of the placebo group and comparisons were not made between each active group to placebo. The sponsor instead shows results of each active group (but not placebo) using DSST "Emax" and "Mean DSST" scores as the dependent variables. The results of mean DSST are shown over time (from baseline to each hourly post-dose assessment until 6 hours post-dose. Results of statistical comparisons are also not shown under Item 9A of the clinstat\clinsum.pdf (pp1691-1692). Finally, the sponsor does not describe results of all dose-levels, only the 3 mg dose-level (the study used several dose-levels above and below the 3 mg dose-level).

Reviewer Comments and Labeling Recommendations Regarding a ' [illegible] Subheading in Proposed Labelng and a Description of Memory [illegible] in Labeling. *The sponsor's proposed title of [illegible] should be changed to subheadings that are standard for this drug class and indication (refer to Sonata® labeling). Therefore, it is recommended that ' [illegible] be changed to subsections on memory [illegible] and on psychomotor/sedative effects. Refer to reviewer's recommended labeling for this section, in blue italicized font provided later.*

It is recommended that the following paragraph that the sponsor proposes for this section of labeling be moved to the

"

ent." However, the following sentences were deleted since they

ult to

first 7 days of treatment and did not recur."

Under

described first (Study 190-001). The following paragraph is proposed for describing this

The results of 190-024 are more accurately described, since most memory tests showed numerically greater impairment in eszopiclone groups compared to placebo, in which failure to reach a level of significance is most likely due to the small sample size (based on examination of efficacy results in summary tables in the study report, Tables 11.4.1.2.2-1 and -2 of the study report of the NDA submission, copies of these tables are also shown as Tables VIA7 through VIA9 in the Clinical Review of the original NDA submission). Table VI10-12 in the original review also show the sponsor's results of 190-025 and the results of the study on learning effects described in paragraph 3 of the recommended labeling below.

Results of composite scores, such as the Power of Attention are difficult to interpret. The sponsor should describe results of individual tests of attention: simple and choice reaction times, digit of vigilant detection speed scores and results summarized in the psychomotor/sedative subsection of labeling below.]

Reviewer Labeling Recommendations (in blue underlined and italicized text) for the sponsor's proposed labeling subsection on under the labeling heading of "Studies Pertinent to Safety Concerns...Drugs."

The following subheadings and text are recommended for labeling to replace the sponsor's proposed title and subsection of

Studies Pertinent To Safety Concerns For Sedative/Hypnotic Drugs

Item 9A on Surrogate EEG Measures. The sponsor responds to the Approvable letter comments regarding EEG measures as surrogate makers. The sponsor replies by acknowledging that EEG results are not recognized as surrogate markers for the purpose of labeling.

Reviewer Comments/Labeling Recommendations. *Despite this acknowledgement, the sponsor describes EEG results in a section of labeling as described under Item 8, above, which would need to be deleted to be consistent with the Agency view on EEG measures.*

Labeling Item 9B on Primary and Secondary Efficacy Claims.

INDICATIONS AND USAGE:

[Claims of more than the primary and key secondary variables are not usually included in labeling.]

Response. The sponsor indicates that their proposed labeling complies with the above. They refer to the following paragraph as being in compliance ' — is indicated for the treatment of insomnia

in controlled outpatient and sleep laboratory studies. — administered at bedtime decreased sleep latency and improved sleep maintenance."

Reviewer Conclusions and Labeling Recommendations Regarding Item 9B. *Review of the sponsor proposed labeling under "Clinical Trials"* —

/ *It is recommended that the sponsor revise the Clinical trial descriptions to only describe primary and key secondary variables which the sponsor list as being the following in the current submission:*

- *Study 190-046: Objective LPS as the primary variable and objective sleep efficiency and objective WASO as key secondary variables*
- *Study 190-047: Objective LPS and sleep efficiency as co-primary variables and objective WASO as the key secondary variable.*

The sponsor does —

— *in proposed labeling. Refer to the Clinical Review and Biometric Review of the original NDA for more details.*

While the sponsor's proposed labeling does —

— *he sponsor refers to the sleep efficiency variable, as a sleep maintenance variable. It is recommended that only the actual primary and key secondary variables are described and that other words are not used to substitute the actual variable. Therefore, sleep maintenance should be deleted and replaced by the actual variable (if it is a key secondary or primary variable).*

The "Elderly" subsection under "Clinical Trials" indicates that 292 subjects were in the "other" study. However, this study (Study 190-0487) had only 264 subjects in the 2 mg and placebo groups. The other 28 subjects were in a 1.5 mg group and this treatment group was aborted prematurely for non-safety related reasons. It is recommended that

/

Finally, it is recommended that the Indications and Usage Language section of labeling be replaced with the following paragraph: —

/

Item 9C-E on Adverse Reactions Bracketed Labeling Comments. The following sections of labeling and italicized comments were included in the Approvable Letter to which the sponsor responds under Items 9C-E in their response submission.

ADVERSE REACTIONS:

The premarketing development program for ESTORRA included eszopiclone exposures in patients and/or normal subjects from 2 different groups of studies: approximately *[provide number]* normal subjects in clinical pharmacology/pharmacokinetic studies; and approximately *[provide number]* exposures from patients in placebo-controlled clinical effectiveness studies, corresponding to approximately *[provide number]* patient exposure years. The conditions and duration of treatment with ESTORRA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse Events Observed At An Incidence Of ≥2% In Controlled Trials

[Please revise the following table. We believe the incidence of adverse events in the controlled trials can best be displayed in — tables.

Also, after the table, please list those ADRs that have a greater than 2% incidence on drug that were not more frequent than placebo.]

Other Events Observed During The Premarketing Evaluation Of ESTORRA

[Please exclude terms in this list that appear elsewhere in the adverse events section.]

Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful *[Is there any pre-marketing experience with ESTORRA or post marketing experience with zopiclone supporting flumazenil's usefulness?]*. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. *[Please explain if there is something specific about ESTORRA that warrants the following sentence in labeling]* — The value of dialysis in the treatment of overdosage has not been determined.

<u>Sponsor's Response to Labeling Item 9C and Reviewers Recommendations regarding Enumeration of Subjects:</u> The sponsor inserts the number of subjects in trials, as requested in the first paragraph under ADVERSE REACTIONS, except for following is recommended regarding one of the numbers inserted by the sponsor (italicized to indicate reviewer comments and recommendations):

> *As specified in the approvable letter the enumeration of "normal" subjects in clinical pharmacology/pharmacokinetic studies should be indicated and should not include hepatically impaired, renal function impaired and other such populations that are not generally healthy population. Therefore, the number 400 in this section (which includes subjects in studies with medically ill subjects, such as in Studies 190-016 and others)*

The following is a copy of the table in the sponsor's response to 9C regarding exposure expressed in patient years, which was calculated for the Phase II and III trials, combined.

Table 9C-3 Total Patient Years of Eszopiclone Exposure in Phase 2/3 Controlled Studies

Astorra Subjects Only	N	Days Follow Up	Years Follow Up
All Ph. II/III (Excluding. 190-049):	951	15615	42.75
190-049 DB	593	80342	219.96
Total	**1544**	**95957**	**262.71**

Response and Reviewers Comments Regarding Labeling Item 9D on Tables 1, 2 in the "Adverse Reactions" Section and of the Geriatric Use section that Refers to Table 2. *The following are comments regarding Labeling Items 9D. The AE tables are provided by the sponsor (Tables 1 and 2) in the "Adverse Reaction" section of proposed labeling. These tables are acceptable to this reviewer as described in the following with some exceptions with recommendations that follow. Before describing the exceptions and providing recommendations the tables are otherwise acceptable as follows. The incidence of AEs for Studies 190-047 and 190-048,*

. The selection of the 6-week non-elderly trial (190-046) for providing results for non-elderly subjects is a reasonable choice since the study uses a fixed dose parallel group design of two different dose-levels, including the recommended dose-level. Furthermore, the study was longer than just a few days as in other shorter term non-elderly efficacy trials. Study 190-049 was much longer (6-month double-blind phase) and only had 3mg daily dose-level. Therefore, it would not appropriate to combine the results of this longer term trial to results of a 6-week trial (studies had other differences). Refer to the Clinical review of the original NDA for additional comments regarding safety that are not provided in this review.

Another observation regarding Table 1 is that the table has infection under Respiratory System, yet the summary table in the original submission for Study 190-049, has infection under Body as a Whole, while the incidence for each treatment group for this event is the same in both of these tables. The sponsor clarified the reasons for differences and similarities between these tables regarding upper respiratory system and Body as a

Whole infections in a 930/04 submission. Based on their explanation the incidence for these events in Table 1 of proposed labeling appears to be reasonable.

The following are reviewer Labeling Recommendations regarding Tables 1 and 2 under Adverse Reactions in proposed labeling:

A consult from the Division of Reproductive Urological Drug Products regarding gender specific AEs (gynecological AEs) was requested and input is pending at the time of this writing (refer to Item 1 of this review for further details).

Reviewer Comments Regarding the Geriatric Use Section of Labeling Regarding Safety Findings

The following is recommended regarding the geriatric use section:
It is recommended that the geriatric use section

Refer to additional labeling recommendations regarding the geriatric population elsewhere in this review.

Labeling Item 9E on "Other Events...During the Premarketing...".
This item pertains to excluding AE terms in the "Other Events ...During the Premarketing..." section of labeling that appear elsewhere in labeling. The sponsor indicates redundant terms are now excluded, as well as other terms (e.g. vague terms, terms commonly observed in the population, events for which a drug cause is remote).

Reviewer Comments and Labeling Recommendations Regarding Item 9E.
A review of the terms that were deleted in this section of labeling generally revealed deletion of terms that appear elsewhere in labeling with a few exceptions in which the following are recommended:

1. *It is recommended that the sponsor provide a rationale for deleting*

This section of labeling also had

Item 9.F Regarding Overdose Treatment

This Item has two subtopics on overdose, such that each subtopic is described separately, below.

Item 9 F on the Subtopic of Experience Supporting the Use of Flumazenil in Overdose Situations.

[Is there any pre-marketing experience with ESTORRA or post marketing experience with zopiclone supporting flumazenil's usefulness?]

Response

The sponsor states that there is no premarketing experience with eszopiclone regarding the usefulness of flumazenil in patients that overdose with eszopiclone. The sponsor could not find any reference to flumazenil in postmarketing summaries of zopiclone that were provided by Aventis.

Case reports of usefulness of flumazenil were found and described as in the following (copied from the submission):

- A 55-year-old man was admitted unconscious following overdose. A benzodiazepine overdose was suspected and a bolus of 200 µg of flumazenil was given IV. The patient rapidly regained consciousness and admitted to overdosing with zopiclone. He subsequently lost consciousness but was again rapidly recovered by a second infusion of flumanzenil.[4]

- A 27-year-old male was found unresponsive, next to empty packets of zopiclone. On route to the emergency department he received 2 mg IV naloxone without effect. In the emergency department, the patient became alert following 0.2 mg flumanzenil.[5]

- In 5 cases of acute voluntary intoxication by zopiclone (alone or in combination with benzodiazepines), flumanzenil was found to antagonize the central nervous system depressive effect and enable rapid revival.[6]

Reviewer Comments and Labeling Recommendations.

The above case reports support the usefulness of flumazenil for patients that overdose with eszopiclone, which is not an unexpected finding given the drug class and pharmacological properties of flumazenil. Therefore, it is recommended that labeling include a description for the use of flumanzenil for treating overdosed patients, as described for other approved drugs in the drug class (refer to Sonata ™ labeling).

Item 9F on the Subtopic of Withholding Sedating Drugs in Overdose Situations.

[Please explain if there is something specific about ESTORRA that warrants the following sentence in labeling]

Response. The sponsor indicates that the above sentence is deleted and is shown as deleted in the highlighted version of the sponsor's proposed labeling (as shown in the labeling\other.pdf file).

Item 9G Regarding Statements on Memory Impairment and Timing of Treatment in the "Information For Patients..." Section of Labeling.

[Please provide your rationale for the statement "memory problems can be avoided if you take ESTORRA only when you are able to get ' — sleep before you need to be active again." You previously stated that there was no formal evaluation of memory function (anterograde amnesia) during the ESTORRA development program. Your annotated labeling refers to section 8./10.H.11.1 MEMORY IMPAIRMENT in the integrated summary of safety; however, this section offers little to suggest that any potential cognitive or psychomotor effects have disappeared at any particular time point after drug dosing. Since the half-life of the drug is 6-hours, one would assume that, based on plasma half-life alone, there would be residual drug effects at a time point that coincides with only one half-life after dosing. This might be more of a problem with a 3 mg dose.]

Safe Use of Sleeping Medicines:

5. **Do not take ESTORRA unless you are able to get** ***Please justify how you concluded that — was sufficient]*** **of sleep before you must be active again.**

Sponsor's Response to Item 9G on Statements pertaining to Time of Treatment and Memory Impairment. The sponsor revised statements that recommend — — of treatment under the "Memory Problems" subsection and in item 5 under the "Safety Use of Sleeping Medicines" in the patient information section of labeling as follows. The phrase ' — was changed to the recommendation for a "full night of sleeping". Therefore, the statement "memory problems can be avoided if..." was changed to the following statement (as shown in their response to Comment 9G and in their highlighted version of proposed labeling in the labeling\other.pdf file):

"In most cases memory problems can be avoided if you take ASTORRA only when you are able to get a full night of sleep before you need to be active again."

Upon review of the highlighted version of proposed labeling, Item 5 under "Safety Use of..." subsection was also found to be revised to indicate that the drug not be taken unless "you are able to get 8 or more hours of sleep before you must be active again" (which previously recommended — These changes were found in the highlighted version of proposed labeling (in the labeling\other.pdf file).

In response to Comment 9G, the sponsor also refers to results of Studies 190-024 (in healthy adults), 190-025 (patients with insomnia) and results of the 6-week Chronic Insomnia study, Study 190-046 to support the above proposed labeling statement.

A "daytime pharmacokinetic study" is also mentioned in the sponsor's response. According to the sponsor, this study showed that DSST effects were "reversed between 5-6 hours after administration of 3 mg." The number of this study could not be found in this response.

Reviewers Comments, Conclusions and Labeling Recommendations.
It appears that the above pharmacokinetic study to which the sponsor describes is Study 190-001 which was a study on healthy adults and is described under Item 9A above.

Item 9A also describes results of studies 190-024 and 190-025. This Item is regarding the sponsor's labeling section on " *but actually encompasses sedative, psychomotor and memory impairment, in which this reviewer recommends changes in the subheadings to parallel standard language for the drug class (as found in Sonata® labeling) and to parallel the actual study results (as previously described under previous items).*

As discussed under Item 9A, at least trends for impairment were revealed on tests that involve speed, memory, as well as psychomotor function that included time points of 9.5 and 12.5 hours. Furthermore, impairment on practice effects in Study 190-046 was also observed on test days (placebo group showed practice effects while the eszopiclone groups showed numerically diminished or absent learning effects on daytime DSST testing on Day 29 of treatment for the 2 mg group and on all DSST test days in the 3 mg group; on Days 1, 15 and 29 of treatment). Note that Study 190-046 was conducted on patients with Chronic Insomnia.

Therefore, it is recommended that the sponsor's proposed statement be deleted and that the patient information section of labeling include a description such as the following.

IV. Updated Safety-Related Items in the Approvable Letter (Items 10-16).

<u>Items 10-14 on the Safety Update.</u>

These items pertain to comments in the approvable letter that pertain to an update on safety information.

Response to Item 10-14 on the Safety Update
The sponsor provides a Safety Update report of only one completed trial in patients and of blinded, ongoing studies of which the sponsor concludes that no new or

unexpected safety findings were revealed. Safety data from the completed — study was not pooled with results of Chronic Insomnia trials described in labeling (such as the incidence of adverse events), since this study involved a different patient population.

The following italicized section summarizes the safety results in the Safety Update report from the reviewer's perspective (thus, this text is italicized). Reviewer conclusions and labeling recommendations are also provided in the italicized paragraphs below. Lastly, a more detailed description of safety findings is provided, which is primarily non-italicized text, but some paragraphs are italicized reviewer comments.

Reviewer Comments, Summary of Safety Update Findings and Recommendations (Items 10-14).

In summary, no new, unexpected safety findings were generally revealed in the Safety Update of completed and ongoing trials that change the overall safety profile of the drug, as previously described in the Clinical Review of the NDA.

The safety data in the safety update report is "preliminary" and "unaudited." Narratives of SAEs and ADOs were provided.

The sponsor only has one completed small study since the submission of the original NDA (and before the May 14, 2004 Safety Update cut-off date). This 2-nightly treatment cross-over study was conducted on 22 randomized patients with — and revealed no SAEs or ADOs.

Two of the five ongoing blinded trials had only approximately 30 randomized subjects in each study and had no reported SAEs or ADOs. Thus, all SAEs and ADOs occurred in the other three ongoing/blinded trials.

Most events were likely to be unrelated to the study drug (while noting the study drug remains blinded). These events were probably not drug related, given the nature or timing of the event, the presence of a pre-existing condition, or the given event may be expected (or was unique) for the study population, or the given event was isolated such as an SAE of cerebrovascular accident (while study drug remains blinded).

Other events were not unexpected for the study drug or drug class, or were similar to those previously described in the original review.

The following summarizes the most remarkable SAEs. These SAEs either do not change safety concerns already discussed (as in the clinical review of the original NDA), or were isolated events (in the absence of causal or contributory factors), or only occurred in a few subjects in which the role of the study was unlikely (for reasons provided below). It is also important to note that the study drug remains blinded in all reported SAEs and ADOs in this safety update.

SAEs of Breast Neoplasia or Breast-tumor. *Since neoplasia is a potential concern, the following SAE of neoplasia is noted. A subject had a positive breast mass biopsy revealing malignancy. This subject had evidence for a pre-existing condition (a "lump" was found one year prior to the study and mammography at study entry was "suspicious). Furthermore, this event occurred among an estimated number of 336 ESZ and 168 placebo randomized subjects in a 6-month Chronic Insomnia study. However, the diagnosis was not made until after 3 months of treatment (that remains blinded), such that the possibility for progression of the preexisting condition or conversion to malignancy, requires consideration (unless the subject was found be in the placebo group). This subject is described in more detail under SAEs for Study 190-059 (subject 0392-022).*

Further consideration is also needed regarding the SAE of a malignant breast tumor in light of a potential drug effect on reproductive hormones and a potential signal for breast related or gynecological event, as described in the Clinical Review of the original NDA and elsewhere in the current review. A consult from the Division of Reproductive Urological Drug Products was requested and a consultative review is pending at the time of this writing.

Given that a number of breast related events observed in trials, as well as concern of neoplasia, the following subject is described. A female subject (after 22 days of treatment that remains blinded), was found to have a breast cyst diagnosed by her "breast" surgeon (mammogram and ultrasound were "negative") and the event resulted in early study withdrawal.

SAEs of chest pain/coronary artery events. *SAEs of chest pain/coronary artery events are not expected for the study drug or the drug class and this event occurred in 4 out 504 randomized subjects in the 6-month Chronic Insomnia trial (2:1, ESZ:placebo, Study 190-050). 2 subjects had a negative cardiac work-up, while the other 2 subjects had pre-existing conditions or risk factors. One of these latter two subjects required "emergency open heart surgery"(the subject complained of dyspnea). As for all subjects with reported SAEs and ADOs reported in the submission, the study drug assignment (placebo or ESZ) in these 4 subjects remains unblinded. These subjects are described in more detail in the subsection of SAEs in Study 190-050.*

A cardiovascular-related safety signal was not described in the original NDA (refer to the Clinical Review in the original ND), other than small trends for decreased blood pressure and increased heart rate that would not be anticipated to result in clinically remarkable outcome. In the 6-month DB phase of Study 190-049 there were 3 SAEs and 3 ADOs (one of these ADOs was also an SAE) of chest pain in ESZ subjects (0.5% of each) and 1 SAE and 2 ADOs of chest pain in placebo subjects (0.5% and 1%, respectively). The narratives of these events in ESZ subjects were re-examined for the purpose of this current review and the following summarizes the nature of these events. The SAEs and ADOs of chest pain in ESZ subjects were observed in patients with pre-existing conditions and/or risk factors, and/or did not recur when treatment was resumed, or the nature of the chest pain was not consistent with a cardiac origin.

Similar to observations described in the review of the original NDA, VSS results in the current submission (under Item 6) showed small trends for outliers on low systolic and diastolic blood pressure in both non-elderly adults and elderly subjects.

Examination of results on orthostatic hypotension outliers in the current submission revealed a signal on the incidence of subjects with orthostatic hypotension in elderly subjects, while non-elderly subjects failed to show a clear signal for a drug effect. However, this observation in elderly subjects was only found at the higher dose levels of 3 and 5 mg daily (17 to 33% of subjects, N=6/group) following single or multiple doses. The incidence of outliers in the lower dose-levels of 1 mg and 2 mg daily was 0% (these are the recommended daily dose levels for elderly subjects). Only one subject with orthostatic hypotension had symptoms (dizziness) and no subjects had syncope.

An SAE of Cerebrovascular Event. *The SAE of cerebrovascular accident occurred in a 58 year old female after 70 days of treatment leading to study withdrawal and hospitalization, in which no risk factors (other than age), no pre-existing condition, or concomitant medications were described in the narrative. In the absence of a known etiologies or contributing factors, a potential role of the study drug requires further consideration. Yet, the study drug remains blinded at this time. Furthermore, this SAE appears to be an isolated event, as it occurred in one subject out of 504 randomized subjects in a 6- month study. Finally, safety findings described in the original NDA did not reveal a signal for this type of an event or a related cardiovascular type of safety signal.*

Previous sections of this review describe additional vital sign data.

An ADO of mild thrombocytosis. *One subject in one of the larger trials was an ADO due to mild thrombocytosis, but this event resolved and was mild (study drug is blinded).*

Reviewer Labeling Recommendations Regarding the Above Safety Update Information of Ongoing and Recently Completed Trials.
This reviewer agrees that adverse event data from the single completed study on — — study should not be pooled with adverse event data from the Chronic Insomnia trials already described in proposed labeling, given that the trials differed in many respects including the one major difference in the patient population.

Refer to the final section of this review for further comments, conclusions and recommendations.

Detailed Description of Safety Update Information of Completed and Ongoing Trials (Items 10-14).
A summary of the results was previously provided, along with reviewer conclusions and recommendations. The following paragraphs describe the safety results in more detail with some italicized reviewer comments following specific aspects of the results or regarding the sponsor's comments or conclusions (as specified).

Section A below describes the database examined for the Safety Update information. The focus of this review is on deaths, serious adverse events and adverse dropouts which are described in Sections B, C and D, respectively.

A. Database of the Safety Update Information.
Since the NDA was filed the sponsor has 6 clinical trials that were conducted under the NDA.

Only one of these trials is completed, Study 190-028 which is a 2-nightly, placebo controlled cross-over study in 22 randomized patients (21 completers) with

The other five trials remain blinded and ongoing and are listed below:

- Study 190-050: A 6-month double-blind placebo controlled trial in patients with primary insomnia. 504 subjects were randomized (2:1) to 3 mg or placebo po Qhs (no completers and 55 early withdrawals).
- Study 190-029: A study of sperm motility in healthy males (92 randomized subjects).
- Studies 190-052 (133 randomized subjects), -054 and -055 (with no more than 35 randomized subjects in each study) are short term trials (up to 8-weeks of double-blind treatment) in patients with insomnia

The cut-off date for this update report is May 14, 2004.

Safety data from the ongoing trials is described as preliminary, unaudited data.

Since there were no adverse dropouts in the one completed trial (Study 190-028), CRFs were not provided in the submission.

Instead of providing CRFs for serious adverse events and adverse dropouts in blinded ongoing trials, the sponsor provided narratives.

The sponsor did not re-tabulate safety data tables (e.g. AE tables) since the only unblinded and completed trial, was Study 190-028 which was conducted on patients with rather than on patients with the proposed indication for approval (Primary or Chronic Insomnia).

Reviewer Comment *Given the study population examined in Study 190-028, it is appropriate not to pool data with safety data from the Primary Insomnia or Transient Insomnia trials.*

Section B. Deaths. No deaths were reported in Study 190-028 and in the 5 ongoing trials.

Section C. Serious Adverse Events

Serious Adverse Events of the One Completed, Unblinded Study (Study 190-028) of 22 Randomized Sleep Apnea Patients.

No serious adverse events (SAEs) were reported.

Serious Adverse Events in Ongoing, Blinded Trials.

Study 190-050: A Large Primary Insomnia, 6-month, Placebo Controlled Study of 504 Randomized Patients:

A listing of SAEs is provided in a summary table later in the section of the review. First, events and brief narrative descriptions are summarized below. Several of these events resulted in cessation in treatment.

One of the events was a malignancy of the breast (so 1 malignancy/an estimated 336 subjects randomized to 3 mg ESZ Qhs and an estimated 168 placebo randomized subjects).

"Malignant Lump in Left Breast" which is the SAE term for subject 0392-022 who had discovered a lump in her breast approximately 9-10 months prior to the study and had a mammogram conducted prior to study entry that was "suspicious". Approximately, 3 months after starting double-blind study drug, a biopsy was conducted and revealed malignancy. The subject underwent mastectomy and withdrew from the study.

Reviewer Comment Regarding this SAE: *The study had 303 randomized female subjects (all male and female subjects were randomized to ESZ or placebo in a 2:1 ratio). Given the sample size of subjects, the pre-existing findings in this subject and a treatment duration of only 3 months (in which the study drug remains blinded) it is likely that this event is not drug-related.*

The first subject listed in the table with pneumonia, had pneumonia at screening. Subject 0415-016 had pneumonia with a fever of 103 degrees (at 28 days after the last dose of study drug) that required hospitalization. However, treatment with the study drug was discontinued (approximately after 1 week of treatment) because of hyponatremia (128 meq/L) of unclear etiology.

Reviewer Comment: *A safety signal for pneumonia or a signal for hyponatremia was not revealed in Chronic Insomnia trials (refer to the review of the original NDA). Therefore, the above events of pneumonia and hyponatremia in the above described patient is likely to be isolated(no SAEs or ADOs of pneumonia in Chronic Insomnia trials as shown in summary tables in the clinical review of the original NDA).*

However, a drug-related effect on incidence of upper respiratory infections and in some studies for other type of infections was revealed, as discussed under Item 2A, with reviewer labeling recommendations.

Chest Pain/Coronary Artery Disease Events: A total of 4 out of 504 randomized subjects had chest pain, chest discomfort or coronary artery disease.

Discrepancies between the summary table listing the SAEs (provided by the sponsor and shown above) and the narratives are noted in which the SAE terms appeared to be inadvertently switched between 2 subjects in the summary table, as described in the following. Note that the summary table has "chest pain of musculoskeletal origin" listed as the SAE for subject 0470-004 (found on page 27 of the clinstat/iss/iss.pdf file), yet the narrative of this subject (found on page 31 of the same pdf file) has the event listed as "coronary artery disease" and no mention of musculoskeletal origin. Instead, this subject required "open heart" surgery based on the narrative (this subject is described in more detail later). Another subject (Subject 0480-033) is listed in the summary table as having the SAE of "coronary artery disease." The narrative for this subject has "chest pain" and indicates that the chest pain was diagnosed in the emergency room as musculoskeletal in nature. This patient was treated with Flexeril and Vicodan. Therefore, it appears that the SAE terms of these two subjects were inadvertently, switched in the summary table.

The 4 SAEs of chest pain or coronary artery events are described in the following, based on a review of the narratives. Two SAEs were negative for cardiac events (both had negative work ups for cardiac disease and one was treated for musculoslelatal pain), the other 2 occurred in males with risk factors or pre-existing conditions in which the one of the subjects required "emergency open heart" surgery and the other subject had a positive work-up for "coronary artery disease" (CAD).[2]

Cerebrovascular accident (CVA) occurred in a 58 year old female after 70 days of treatment leading to study withdrawal and hospitalization, in which no risk factors (other than age), no pre-existing condition or concomitant medications were described.

Reviewer Comment regarding this CVA SAE: *In the absence of more information the relationship of this event with the study drug may be likely but the study drug is blinded (subject may have been in the placebo group). More information should become available as this subject is followed that may shed further light on contributory or causal factors. Yet, this event is isolated (no other SAEs of cerebrovascular event were reported in other trials reported in this submission or reported in trials of the original NDA, as described in Section VIII of the Clinical Review of the original NDA).*

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[2] In more detail, 2 male subjects had diagnostic findings for coronary artery disease (S 0472-004 and S 0470-004). One subject required emergency "open-heart" surgery after presenting with dyspnea one day after his last dose of treatment. Both men were over 50 years old and generally had pre-existing conditions or risk factors for coronary artery disease. The third subject was a 53 year old female subject (04830-033) with chest pain for several days. The emergency room work-up was negative for cardiac disease (2 negative ECGs and a negative chest x-ray) and she was treated for musculoskeletal pain. The fourth subject was a 35 year old male, hospitalized for chest pain after 150 days of double-blind study drug, who had "no ECG or biochemical evidence of cardiac ischemia."

Listing of Serious Adverse Events in Study 190-050

Manufacturer's Case control #	Subject ID #	Event
2004SP000008	0396-006	Pneumonia
2004SP000040	0458-003	Worsening of joint pain
2004SP000047	0472-004	Left chest discomfort
2004SP000048	1040-013	Acute appendicitis
2004SP000051	0454-008	Cholecystitis
2004SP000067	0478-005	Cerebrovascular accident
2004SP000070	1045-017	Chest pain
2004SP000080	0480-033	Coronary artery disease
2004SP000082	0470-004	Chest pain of musculoskeletal origin
2004SP000084	0392-002	Right basal pneumonia
2004SP000090	1095-012	Malignant Lump in left breast

Study 190-029: A Sperm Motility Study with 92 Randomized Males. One SAE of "Amputation of Right 3rd and 4th Fingers

Study 190-052 A Placebo Controlled Study of 133 randomized subjects with Insomnia. One SAE was reported which was upper respiratory tract infection in a 38 year old with history of sarcoidosis.

Studies 190-054 and -055 with only approximately 30 Randomized Subjects in Each: No SAEs in either of these trials (approximately 30 randomized subjects in each trial).

Section D. Adverse Dropouts

Adverse Dropouts in Completed Study 190-028 of 22 Randomized Patients.

None were reported in this sole completed trial.

Adverse Dropouts in Ongoing, Blinded Trials.

Study 190-050 Primary Insomnia, 6-month Placebo Controlled Study of 504 Randomized Patients: Adverse dropouts (ADO) include the following: several ADOs of somnolence or fatigue mild insomnia, one ADO of depression in a patient with pre-existing depression and other psychiatric conditions, headache (2 Ss), GI upset (1S), back pain (1S), unpleasant taste (1), worsening of diabetes (1S, this event continued after

treatment cessation), a transient globus sensation (primary term: dysphagia) in which treatment was not stopped, but was later stopped when fatigue and arthralgia were reported (stopped on Day 49), erectile dysfunction (in a 48 year old after 7 days of treatment), elevated thyroxine (which continued after stopping the drug), syncope (in a 60 year old taking atenalol, hydrochlorthiazide, later found to have hypokalemia).

Study 190-029: A Sperm Motility Study of 92 Randomized Subjects: No adverse dropouts (ADOs) were reported.

Studies 190-052: A Placebo Controlled Study of 133 Randomized — Patients with Insomnia. The following were the ADOs reported in this study (in 1 subject each, unless otherwise specified): insomnia, increased agitation, headache and nausea and accidental injury. Additional events are described in the following.

A 45 year old female reported a lump on her breast on Day 22 of treatment, but mammography, ultrasound were negative and a "breast" surgeon gave the diagnosis of breast cyst.

The following are additional ADOs, due to their unexpected nature (in the opinion of this reviewer) in the absence of underlying conditions, risk factors or non-drug related etiologies.

Sexual dysfunction was reported in 3 males on Days 3, 4 and 8 of treatment. One subject had mild thrombocytosis on the day of randomization which resolved after 2 weeks (levels drawn one week after receiving one week of study drug).

Reviewer Comments Regarding Unexpected ADOs of Sexual Dysfunction. *Sexual dysfunction is unexpected for the study drug or drug class, yet it occurred in 3 subjects. A total of 133 subjects were randomized to blinded study drug. Safety findings of trials for the Chronic Insomnia program did not include a signal for sexual dysfunction (as described in Section VIII of the Clinical Review of the original NDA). It is likely that these events are unique to the study population (not observed in other populations) and may be expected event in this particular patient population (— patients). Furthermore, the study drug remains blinded.*

Studies 190 -054 and -055 with Approximately 30 Randomized Subjects in Each: No ADOs were reported in these two studies.

Item 15. Worldwide Experience with Eszopiclone

Approvable Letter Comment

Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Response to Item 15 on Worldwide Experience

The sponsor only describes experience with zopiclone and not with eszopiclone, since the latter has not been marketed (see Item 16 below).

Reviewer Comments Regarding Worldwide Experience (Item 15)
Zopiclone postmarketing data was previously reviewed by the Safety Group with their primary focus on neoplasia.

In the current submission the sponsor identified no cases of neoplasia in the updated period report review or in a literature review for neoplasia.

Item 16. English translations of Foreign Approved Labeling for Eszopiclone
Approvable Letter Comment
Provide English translations of current approved foreign labeling not previously submitted.

The sponsor explicitly states under Item 16 of the response submission (on page 1008 of the clinstat\iss.pdf file) that "eszopiclone is not marketed din any country at this time." However, copies of English translations of approved foreign labeling for zopiclone are provided in the submission.

The racemic drug has not been withdrawn from the market due to regulatory reasons (any discontinuations from the market were due to "commercial decisions").

The following additional information regarding the foreign marketing of the racemic drug is provided in the submission (the sponsor obtained this information from Aventis):

- A list of 65 countries in which the racemic drug is currently marketed
- A list of countries where the drug is not marketed (either discontinued or never marketed)
- Countries in which Aventis withdrew approved applications.

Reviewer Comment and Conclusions. *The sponsor indicates that eszopiclone is not marketed in any non-US country, such that there is no approved labeling to provide, as requested in the Approvable letter.*

Zopiclone has not been withdrawn from the market due to regulatory reasons, but has been withdrawn for non-regulatory, commercial reasons, as described above.

V. Items Related to Other Specialties in the Approvable Letter (Items 4-5, 17, 18, and 19)

Item 4. Controlled Substance Category
Approvable Letter Comment
We have determined that Estorra should be placed in Category IV of the Controlled Substances Act.
Sponsor's Response to Item 4.
The sponsor acknowledges this classification and includes the Category IV classification in their proposed labeling.

CMC Item 5.
Approvable Letter Comment

You will need to develop a 1 mg tablet strength, or alternatively develop a scored 2 mg strength. The 1 mg dose was clearly effective (for sleep latency) in elderly patients, and should also be used in severely hepatically impaired patients, whose exposure is twice that of normal patients. We believe that it would be important to have available the 1 mg dosage strength for these and other sensitive patients.

This item is under review by CMC and CMC input remains pending at the time of this writing.

Item 17. OCPB items.

OCPB consultant Dr. Andre Jackson has not expressed in unresolved issues from an OCPB perspective. Refer to Dr. Jackson's review of the 6/14/04 submission for details (pending final Team Leader signature at the time of this writing).

Item 18. CMC item.

CMC input is pending at the time of this writing.

Item 19. DMETS, Nomeclature Item.

The DMETS review is pending at the time of this writing.

VI. Pediatric Research

Item 20. Pediatric Research Equity Act (PREA)

The sponsor requests a deferral of pediatric studies of adolescents is requested because . They request a deferral since the indication for adults is currently under review . They suggest a defer date of

A waiver for pediatric studies on younger children (<12 years old) is requested, since the sponsor does not anticipate "that a sleep hypnotic should be considered for this younger group."

Reviewer Comments and Recommendations. *According to a communication between this reviewer and Team Leader, Dr. Paul Andreason (who was also the reviewer of the ., an Advisory Committee meeting was held that recommended that a pediatric indication not be considered for the pediatric population, given that insomnia or a disorder of Chronic insomnia remains poorly understood and ill-defined. It is this reviewer's opinion that insomnia, potential causal factors, diagnostic criteria and diagnostic methods for revealing the etiology and for making a diagnosis in children also requires further development.*

Deferral for consideration in conducting adolescent trials is reasonable given that this NDA is not yet approved and if it is approved at the Agency level, then some

postmarketing experience would be advantageous before considering an adolescent development program. Furthermore, if and when the NDA is approved, consideration should be given to safety concerns that may be identified as needing further Phase IV or postmarketing, epidemiological investigation and that may need to be addressed before considering an adolescent development program.

VII. Promotional Materials

Item 21. Promotional Materials and Advertising, DDMAC Item.
These materials were not included in the submission, as they will be sent later, upon request.

VIII. Overall Conclusions and Additional Key Labeling Recommendations, Not Addressed in Previous Sections

Refer to the Approvable Letter regarding the issues being addressed in this review.

Aside from the concern of neoplasia, the current submission does not describe any remarkable new safety finding that this reviewer considers to be present a non-approvable issue. That is, the current submission does not provide any new reason(s) for considering eszopiclone as not being adequately safe or efficacious for approval of the NDA, as described in more detail below.

In light of the Agency action for giving this NDA an approvable action the following are comments and recommendations to be considered before the Agency grants an approved action on this NDA (comments and recommendations provided in this review are from a clinical perspective).

Key Labeling Issues and Recommendations, not provided in Previous Sections

Refer to previous sections of this review for labeling recommendations relevant to each clinical item and clinical labeling item addressed in the current approvable response submission. The following provides additional key labeling recommendations.

All labeling recommendations in this reviewer are based on labeling proposed by the sponsor in the labeling\other.pdf file (a highlighted version). Annotations to labeling changes were provided in an annotated version (in a pdf file) in the current submission.
The following are the additional key labeling recommendations:

1. **Neoplasia and Gynecological Events.** Consultations were requested regarding neoplasia and gynecological events (from Divisions of oncology and reproductive urological drug products). See questions sent to the consultants in this review, under Clinical Item 1. Input from the consultants.
2. **Sleep Maintenance and other Proposed Efficacy Claims.** Proposed labeling has the terms maintenance under "Indications and Usage" and in other

section of labeling. It is recommended that this section only specifies the indication for , rather than for sleep maintenance for reasons that follow. It is also more accurate to describe actual primary and key secondary variables than to make inferences on validity, specificity and reliability as measures of different aspects of sleep of sleep disturbances. Results of variables that were not declared *a priori* as primary and key secondary variables should not be included in labeling. Finally, the emphasis of treatment should be for (as described in a separate item below).

Proposed labeling specifies that

Under the Geriatric Use Section of labeling indicates tha:

There are several unresolved issues regarding claims of sleep maintenance . (in the opinion of this reviewer), as described in the following paragraphs.

The issue of difficulties ir n sleep maintenance as distinct subtypes of sleep disturbances of Chronic/Primary Insomnia to be included in proposed labeling is complex and the proposed nomenclature sleep maintenance) is not clearly defined in the submission. The following are some additional comments/issues that would need to be addressed:

- The DSM-IV does not specify diagnostic subtypes of sleep disturbances in patients with Primary Insomnia.
- Any proposed nomenclature for labeling needs to be clearly and operationally defined with a clear, established scientific and clinical basis.
- It is not clear if the two subtypes of sleep disturbances (sleep maintenance

The following are some additional concerns regarding the sponsor's trials with respect to making claims in demonstrating efficacy for sleep "maintenance" during the night.

- Aside from the problem regarding established diagnostic criteria for subtypes of Chronic Insomnia and in establishing an adequate characterization of subgroups of Chronic Insomnia patient populations, the sponsor's Chronic Insomnia trials did not distinguish subjects according to the specific types of sleep disturbances or combinations of sleep disturbances (e.g. did not include only one subtype in a given trial or include parallel groups of patient populations with each subtype, and/or combination of subtypes).
- The concern for overlap between various primary efficacy and key secondary variables and whether or not the variables can adequately distinguish (with reliability and validity) between

- The sponsor's proposed maintenanc claims are based on subjective, as well as objective sleep measures. Aside from previous issues, it is not clear if subjective measures reflect the same type of sleep disturbances that are reflected by objective measures (assuming they are specific to a given sleep disturbance). So assuming a given objective sleep measure is valid, specific and reliable in detecting efficacy on a specific sleep disturbance in the Chronic Insomnia population, is there a subjective sleep measure that is also specific, valid and reliable in detecting efficacy on this same specific measure.

Given the concerns, as described above, it is difficult to interpret the results of the sleep measures in objective or in subjective sleep studies with regards to specific sleep effects. A discussion of potential issues, with a rationale as to why such issues were not a concern to the sponsor, cannot be found in the original or current submission.

Instead of adopting new nomenclature and making inferences as to the interpretation of this nomenclature, it is recommended that the language in pertinent sections of approved labeling fo

In addition to the above, also refer to previous items regarding recommended indication and regarding an emphasis or

Alternatively, consideration should be given to an Advisory Committee meeting to address this issue and concerns, as described above.

The above were similar issues raised with the sponsor of IND at meetings with the sponsor and as described in clinical reviews under the IND. This IND was

3. Description of Efficacy Results under "Clinical Trials." As described in more detail under Item 9B in this review, the sponsor describes results on a number of efficacy variables under "Clinical Trials" that included variables that were not primary or key secondary variables. This includes the first paragraph of this section, as well as subsequent sections describing results of specific studies. As previously indicated in the Approvable Letter, it is recommended that the results of only the primary and key secondary variables of each trial in labeling be described for all Phase III trials (elderly and non-elderly) in all relevant sections of labeling.

Furthermore, it is recommended that only the specific primary and key variable term be used and that these terms are not replaced by another word such as in the following examples. Sleep maintenance appears in several places under the description of study results in the "Clinical Trials" section. This term is used in place of the actual variable employed in the given trial (sleep efficiency). Sleep maintenance should be deleted. Any trial using sleep efficiency as a primary or key secondary variable should describe the actual variable, "sleep efficiency" rather than replacing with another term, such as sleep maintenance. See the above discussion regarding additional concerns in making sleep maintenance claims.

Finally, not all key secondary results were positive (reached a level of significance) and should be described as such in labeling. For example, Objective WASO in Study 190-045 showed a p value of 0.328 when comparing the 3 mg group to the placebo group. Revise the description of each study to show the actual study results.

5. Recommended Starting Dose, Maximum Dose in Elderly and Non-Elderly Adults. The starting dose levels should be at the lowest possible efficacious dose, as well as specifying a maximum, not-to-exceed dose-level for non-elderly adults and for elderly adults.

Given the above recommendations, the "Dosage and Administration" section of labeling should include

6. Patient Information Section. The proposed labeling shows few changes in this labeling section from the Approvable Letter version of labeling. However, a few exceptions are noted below. In summary, this section of labeling should reflect other safety concerns and recommendations described elsewhere in this review and in labeling. The following focuses on revisions from those of the Approvable Letter version.

The sponsor's proposed labeling revisions include a change in language describing [redacted] in the Patient Information section are not recommended if the NDA is approved at the Agency level. The sponsor deleted the phrase describing the [redacted]

The revised paragraph (as above) should remain as specified in labeling attached to the Approvable Letter, which is also the [redacted]

Given previous recommendations regarding a maximum recommended dose-level in other labeling sections, it is important to note the following regarding the Patient Information section. This patient labeling section includes a bulleted item under [redacted]

Another revision of the patient information section of labeling is previously described under Clinical Labeling Item 9G in Section III of this review.

[redacted]

8. Accidental Injury. Refer to Section II, Item 2 B for labeling recommendations.

9. Possible New Onset Depression Under Warnings and Precautions. See additional comments below regarding a signal for depression, primarily with long term use, as observed in the longterm study (190-049) in which a number of ADOs of depression occurred in patients that had no prior history. One caveat to interpreting the results on depression is that undiagnosed Major depressive disorder in patients with a chief complaint of insomnia (particularly in the primary care setting) is not uncommon. See a more complete discussion of this observation below and refer to the Section VIII of the original review.

Given the observations of AEs and ADOs of depression, the last sentence of the

10. Hallucinations in Patients with a History of Benzodiazepine Abuse. The Precautions, Warning and Drug Abuse and Dependence sections of labeling should include a description of the high incidence of hallucinations in subjects in a study of this population (refer to Secion VIIIQ of the original review). This is an issue for consideration by CSS.

11. Respiratory Drive Effects. The sponsor describes the results of a respiratory drive study 190-012 in the second paragraph of the "Use in Patients with Concomitant Illness" subsection. It is recommended that this section be revised to

12. Nursing Mothers. The sponsor's proposed labeling indicates that caution should be exercised in treating breastfeeding mothers. However, it is recommended

13. Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs." See previous labeling recommendations under Items 8-9 in Section III of this review. The following are additional recommendations for this section.

a) Under the " subsection on withdrawal AEs. It is recommended that withdrawal AEs (AEs that occurred after cessation of double-blind treatment) in

b) Under the " subsection. In addition to previous recommendations for this subsection it is also recommended that the following statement appear in the last paragraph of this subsection:

14. Recommendations for the Adverse Reactions Section of Labeling

a) Refer to Item 9 in Section III of this review.

b) The section on adverse dropouts ("Adverse Events Resulting in...") under Adverse Reactions should be revised as follows:

- To show the incidence of ADOs for the elderly trials, combined (as the sponsor has done in their first sentence in this subsection of labeling, see the bottom of page 13/14 of the pdf file). However, this sentence should be revised to specify that the

- The second sentence

- The last statement of this section specifies that '

d) Dose related AEs should also be noted under the Adverse Events subsections of labeling using the following criteria: AEs with an incidence of at least 2% in the high dose ESZ group and at [redacted] observed in placebo, and is also numerically greater than the incidence in the low dose ESZ group.

Consequently, Table 1 of labeling should be followed by a [redacted]

15. Drug Abuse and Dependence section in addition to the above recommendation regarding hallucinations, the following is noted. The sponsor changed this section of labeling which deviates from standard language for this section of labeling for the drug class. Dr. Syliva Calderon (the CSS reviewer) recommends standard language regarding tolerance, abuse and dependence.

16. Geriatric Use Section.

Also, see previous recommendations relevant to the section of labeling

18. Inconclusive Thyroid Function Results. In the opinion of this reviewer, thyroid results (as descried in the original clinical review) are inconclusive (in part due to studies not designed to examine thyroid effects) but are not a reason for not considering ESZ treatment unsafe in the population, dose-levels and duration of treatment discussed in this section of this review. Consideration should be given to resolving these inconclusive findings either by seeking consultative input in the Agency or by further investigation and by postmarketing monitoring for related events.

The above recommendations for labeling do not address the issue of neoplasia and gynecological adverse event findings, as consultative input is pending at the time of this writing, as previously discussed in this review.

A Pharmacology Toxicology related Change Proposed by the sponsor.
The following is a change in describing pharmacodynamic properties of the drug in proposed labeling:

The sponsor added the following:

Therefore, consideration should be given to revising this section of labeling as suggested by Dr. Atrakchi.

The following are additional comments regarding potential safety concerns and are additional reasons for [illegible] (as previously recommended):

1. Hyperglycemia and Decreased Platelet Count. The original review describes a possible association between hyperglycemia and decreased platelet count in subjects with supra-therapeutic plasma levels of eszopiclone in special population PK studies (hepatic, renal impairment PK studies). For reasons previously described in the original review, these results are difficult to interpret.

More subtle findings on the incidence of outliers on hematuria and on glucose related laboratory parameters were observed in elderly subjects treatment daily for 2-weeks (see Section VIII of the review of the original NDA).

Other subtle platelet findings were observed in a non-elderly long term trial (190-049), of small magnitude, as previously described.

While potential effects on platelets were small in the above trials, effects on glucose were of sufficient magnitude in the Phase I special population PK trials and these trials included diabetic patients, that one should consider drug effects on increasing glucose in diabetic patients. An SAE (also an ADO) of "new onset diabetes mellitus" was reported in the longterm non-elderly study (190-049) and one of the ongoing longterm Chronic Insomnia trial (190-500) described in Section IV of this review had "worsening" of their diabetes.

2. Psychiatric and CNS Effects

Refer to the original NDA review for details and concerns (Section VIII.Q) in treatment group differences on incidence of CNS AEs (such as agitation, memory impairment of all trials combined, depression and others) appeared somewhat greater in eszopiclone Chronic Insomnia trials than that described for Phase III trials of Sonata™ (refer to approved labeling). Also there were 3 SAEs of agitation or hostile behavior (SAE term in the latter was neurosis) and 5 ADOs of agitation in the 6-month DB phase of Study 190-049. The Warning section of labeling includes precautionary statements relevant to these neuropsychiatric concerns.

One concern is regarding depression during treatment. Depression was an AE in 4.6% eszopiclone subjects compared to 1.5% placebo subjects of the DB phase of the same study and there were 2% ADOs of depression (12/593 subjects) in the eszopiclone group compared to 0 placebo subjects. Most of the 12 ADOs were in patients with no prior psychiatric history. While, it is not uncommon for patients to present with a chief complaint of insomnia to have an undetected, underlying mood disorder, one cannot assume this in these reported ADOs. Therefore, recommendations are made above, regarding the Warning and Precuations section ob labeling.

Confusion and other AEs are previously described in Section VIIIQ of the original NDA review, that were observed even at therapeutic dose-levels several trials whereby a maximum dose-level and treatment duration for non-elderly and elderly adults should be provided in appropriate labeling sections.

4. Tolerance and Rebound Effects. Refer to the original NDA review regarding observations and discussions of potential tolerance and rebound effects (primarily in Section VIB, such as Study 190-046). However, potential tolerance effects, if present, appear to be small. Yet, possible rebound effects would suggest that tolerance could develop. These potential concerns provide further support for the above labeling recommendations fo — or recommended starting dose-levels that are generally the lowest dose-levels in pivotal trials and were found to show significant treatment group effects compared to placebo.

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
P Andreason/K Brugge/R Gujreel/M Mille/T Laughren/A Atkrachi/A Jackson/G Gill-Sangha/N Khin/ S Calderon

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Brugge
10/18/04 06:23:24 PM
MEDICAL OFFICER

Paul Andreason
11/19/04 12:57:22 PM
MEDICAL OFFICER
Please see my memo to the file.

MEMORANDUM

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

DATE: February 24, 2004

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Action on NDA 21-476, eszopiclone (Estorra), for treatment of insomnia

TO: File, NDA 21-476

I. Introduction

Division reviews and memos clearly define what is, and what is not, clear about eszopiclone.

A. It is clearly an effective treatment of insomnia. This has been shown in younger and older patients, for periods up to 6 months, and the dose is reasonably well defined. [I should note that study 045, despite its short treatment periods, seems to me to be an adequate and well-controlled study supporting effectiveness, despite reservations of Drs. Katz and Andreason. It really makes no difference whether a study is "phase 2" or "phase 3," if it's adequate and well-controlled, which this was. I also note our longstanding preference for parallel, rather than x-over studies, and believe it could use reconsideration rather than further endorsement.] Doses of 1-3 mg are all effective and there is at least some evidence that 3 mg is more effective than 2 mg, but with increasing rates of unpleasant taste, lost libido, dry mouth, and perhaps hallucinations and dizziness in the elderly. I believe the starting dose should be 2 mg (1 mg in the elderly). The odd findings of infections and accidental injury deserve further attention, improbably drug-caused as they seem and the human tumors also need further examination. The concern that the unpleasant taste caused by eszopiclone might have unblinded the studies sufficiently to have affected their credibility, while interesting, does not seem persuasive to me, as the rate of this reaction at low doses (where effect is still shown), while still substantial, does not seem nearly high enough to account for the effectiveness seen. I would also be very astonished to learn that there is a placebo response measurable on polysomnography. The analyses of this issue suggested by Dr. Katz (page 12 of his February 20, 2004 review) seem reasonable.

B. The main issue is the possible rodent carcinogenicity. I accept the conclusion of Drs. Rosloff and Atrakchi that the fibromas and sarcomas in male mice and thyroid follicular cell Ca in male rats have been adequately explained and do not represent a risk to humans. This leaves the pulmonary adenomas and adenocarcinomas in female mice and mammary adenocarcinomas in female rats for further consideration.

II. Findings

A. The results of concern in female mice with respect to pulmonary tumors are from a racemate study:

	C_1	C_2	1 mg/kg	10 mg/kg	100 mg/kg
Ad	9.6	7.7	9.6	5.7	19.2
Ca	0	0	1.9	0	3.8
Ad+Ca	9.6	7.7	11.5	5.7	23.1

No early onset.

No tumors in study of eszopiclone at exposures 12 times higher than S-zopiclone in the racemate sudy in a different mouse strain.

The 23.1% is >historical range, but is based on many more sections. In fact, every group in the study, except for 10 mg/kg, but including the two control groups, had adenoma rates outside the historical range of 1.7-6.8%. All groups were within historical rates of carcinoma (0-5.8%).

B. The breast adenocarcinoma results of concern in female rats are also from a racemate study:

	C_1	C_2	1 mg/kg	10 mg/kg	100 mg/kg
Ad+Ca rate	8%	22%	18%	30%	36%

HD is significantly greater than the combined control groups but I believe this is an incorrect analysis. The purpose of having 2 discrete control groups is to allow examination of their variability, a purpose that is utterly defeated by pooling them. (If you wanted a larger control group, just make it larger, don't have 2 groups.) In fact, using C_2, there would seem to be no significant difference between HD and C_2 and (eyeballing) no positive trend test either. Put another way, only one of two identical racemate studies (with common treatment groups but separate controls) had a "finding." Note also that the % difference between C_1 and C_2 (14%) is quite similar to the difference between C_2 and 10/100 (8% and 14%). In other words, and for unclear reasons, the rates of these tumors are highly variable.

The sponsor's explanation – that the drug induces senescence and senescence causes tumors – does not appear very satisfying.

The rat single isomer study at doses up to about 1/2 the racemate dose showed nothing at all.

III. Discussion, carcinogenicity

I believe, as does Dr. Rosloff, who is extremely experienced in these matters, that the carcinogenicity findings are very weak, short of what would be needed to reach a NA conclusion at this stage, and similar to findings in drugs we have approved for symptomatic conditions. (Dr. Rosloff states this too, but we would need to find such cases to support this point fully.)

1. The pulmonary tumors in mice are not seen in a second mouse study at 12 times the exposure of S-isomer (or 6 times exposure to combined isomers). While it is a different

strain, one expects some consistency in results and I believe this substantially weakens the observation, as does also the negative P-53 mouse study.

2. With respect to rat breast tumors, as noted above, the point of having 2 controls is to examine the variability of the control. Indeed C2 is well outside the upper limit of the historical range, greatly weakening the importance of the observation that the mid- and high-dosage groups are outside that range. In addition, the S-isomer study showed nothing at a dose of 50% of the total racemate dose, a dose well above the mid dose of the racemate study. Once again, the racemate finding is not replicable.

I should note that I fully agree with Dr. Katz's conclusion that there is no good reason to accept a human risk for a hypnotic drug with no advantage over alternatives that lack this risk. My conclusion that the drug can be considered approvable is based on my view that 1) the carcinogenicity findings with the racemate are very weak in the first place and 2) are simply not present in the single enantiomer studies. I do not believe that an unreplicated weak finding should lead us to conclude that there is a human risk.

IV. Conclusions

I believe the NDA should be considered approvable for reasons similar to those put forth by Dr. Rosloff and elaborated above. Obviously, any matter on which the pharm/tox and clinical groups disagree among themselves deserves continued attention.

As noted above, the questions posed to resolve the human neoplasia reports (Dr. Brugge's principal reason for recommending NA) should be answered.

[I note that I can't find reviews of the new eszopiclone rat or mouse studies. Also, there appear to have been consultants on the rodent carcinogenicity studies (pharm/tox, page 152); what do we think of their views?]

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/s/

Robert Temple
3/4/04 04:41:46 PM
MEDICAL OFFICER

MEMORANDUM

DATE: February 20, 2004

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-476

SUBJECT: Recommendation for action on NDA 21-476, for the use of Estorra (eszopiclone) Tablets in the Treatment of Insomnia

NDA 21-476, for the use of Estorra (eszopiclone) Tablets in the Treatment of Insomnia, was submitted by Sepracor on 1/30/03. Eszopiclone is the s-isomer of racemic zopiclone, a hypnotic marketed in 85 countries. The sponsor of zopiclone (Rhone Poulenc Rorer) was told by this division a number of years ago that that a [redacted] The issue of carcinogenicity with zopiclone/eszopiclone has been the subject of numerous discussions between the division and Sepracor over time. Based on these discussions, and the sponsor's generation of data that they believe establish that the animal findings with zopiclone are not relevant for humans, we decided that the application could be filed and reviewed. The sponsor submitted data from new carcinogenicity studies with eszopiclone in the last 3 months of the original review cycle, so the current PDUFA due date is 2/29/04.

The application contains the results of 6 controlled trials (5 in patients with chronic insomnia, one in a transient insomnia model), safety data meeting ICH guidelines for exposure at appropriate durations, and the required pre-clinical, CMC, biopharmaceutic, and abuse liability data. The application has been reviewed by Dr. Karen Brugge, medical officer (review dated 9/15/03), Dr. Ohidul Siddiqui, statistician (review dated 11/14/03), Dr. Gurpreet Gill-Sangha, chemist (reviews dated 9/30/03 and 11/6/03), Dr. Aisar Atrakchi, pharmacologist (review dated 2/19/04), Dr. Barry Rosloff, supervisory pharmacologist (memo dated 2/19/04), Roswitha Kelly, statistician (review dated 12/4/03), Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics (reviews dated 9/23/03 and 2/19/04), Dr. Silvia Calderon, Controlled Substances Staff (review dated 11/25/03), Carol Pamer, Division of Drug Risk Evaluation (review dated 9/2/03), Linda Y. Kim-Jung, Division of Medication Errors and Technical Support (DMETS; review dated 12/9/03), Drs. Tamal Chakraborti and Nilufer Tampal, Division of Scientific Investigations, Dr. Ni Khin, Division of Scientific Investigations (review dated 11/10/03), Dr. Gerard Boehm, safety reviewer (review dated 10/8/03), and Dr. Paul Andreason, Psychiatric Drugs Team Leader (memo dated 11/7/03). Drs. Brugge. Andreason, and Atrakchi recommend that the application be Not Approved, though Dr. Rosloff concludes that the pre-clinical data not serve as a reason for a Not Approvable action. In this memo, I

will offer a brief review of the relevant data, and the recommendation of the division for action on this application.

Effectiveness

As noted above, the sponsor has submitted the results of 6 controlled trials; 5 in patients with chronic insomnia and 1 in a transient insomnia model.

1) Study 045 was a 6 period cross-over study, each treatment period of 2 days of treatment, employing doses of 1, 2, 2.5, 3 mg of esz, zolpidem 10 mg, and placebo.
2) Study 046 was a parallel group study in which patients with chronic insomnia were randomized to receive 2 mg, 3 mg, or placebo for 44 days.
3) Study 049 was a parallel group study in which patients with chronic insomnia were randomized to receive either 3mg or placebo for 6 months.
4) Study 047 was a parallel group study in which elderly patients with chronic insomnia were randomized to receive 2 mg or placebo for 2 weeks.
5) Study 048 was a parallel group study in which elderly patients with chronic insomnia were randomized to receive 1 mg, 2 mg, or placebo for 2 weeks.
6) Study 026 was a parallel group study in which normal volunteers were assessed in a sleep lab (transient insomnia model). In this study, patients were randomized to receive 3 mg, 3.5 mg, or placebo.

All studies except for Studies 049 and 048 used as their primary outcome measure Objective Latency to Persistent Sleep (LPS) as measured by polysomnography (PSG). Studies 049 and 048 used subjective sleep latency as their primary outcome measure. The following tables provide the relevant data for the primary outcome measures in each of these studies. The completion rate in all studies, save Study 049, was 90% or greater. In Study 049, the completion rate was about 60% in both treatment groups.

Study 045

	1 mg	2 mg	2.5 mg	3 mg	Zol	Pbo
N	63	63	65	64	64	63
Mean	25.2	20.1	18.6	18.3	16.6	37.8
P-value	<.0001	<.0001	<.0001	<.0001	<.0001	

Study 046

	2 mg	3 mg	Pbo
N	104	105	99
Mean	23.0	18.0	33.0
P-value	<.0001	<.0001	

Study 047

	2 mg	Pbo
N	136	128
Mean	19.3	40.8
P-value	<.0001	

Study 26

	3 mg	3.5 mg	Pbo
N	98	96	98
Mean	9.1	6.6	17.9
P-value	<.0001	<.0001	

Study 049

	3 mg	Pbo
N	593	195
Mean	46.7	64.7
P-value	<.0001	

Study 048

	1 mg	2 mg	Pbo
N	70	79	79
Mean	54.7	50.7	87.6
P-value	.009	.003	

The following p-values were obtained in the following studies for the key secondary outcome measures, Objective Sleep Efficiency (OSE), Objective Wake Time After Sleep Onset (WASO), and Subjective Total Sleep Time (TST):

	1 mg	2mg	2.5 mg	3mg	3.5 mg	Pbo
Study 045						
OSE		<.0001	<.0001	<.0001		
WASO		.018	.012	.33		
Study 046						
OSE		.0059		<.0001		
WASO		.26		.0055		
Study 049						
TST				<.0001		
Study 047						
WASO		.035				
Study 048						
TST	.27	.0003				
Study 026						
OSE				<.0001	<.0001	

Safety

A total of 1839 subjects received at least one dose of eszopiclone; 1076 subjects received at least one dose of 3 mg. A total of 360 patients received 3 mg for at least 6 months, and 296 patients received 3 mg for at least 1 year.

There were no deaths in patients receiving eszopiclone in the NDA database. There were few serious adverse events reported in controlled trials that could reasonably be attributed to treatment. There were 18/593 (3%) SAEs in drug treated patients in Study 049 (6 month controlled trial) compared to 2/195 (1%) in placebo patients. No single ADR among these in the drug-treated group occurred in more than 3 patients (chest pain, GI disorder [2 appendicitis] occurred in 3 patients each; agitation occurred in 2 patients).

Adverse Dropouts

In the 6 month study (Study 049), 13% of patients discontinued due to an adverse event compared to 7% of placebo patients. Only Depression occurred in at least 2% of eszopiclone treated patients and with an incidence twice that of the placebo patients. No single adverse event responsible for discontinuation met these criteria in the other controlled trials.

Adverse events

The following chart displays the adverse events occurring in at least 2% of eszopiclone treated patients with an incidence at least twice that in the placebo patients in the 2 week studies in elderly patients:

ADR	ESZ N=315	PBO N=208
Unpleasant taste	10%	1%
Dry Mouth	5%	2%
Dizziness	4%	2%
Pain	4%	2%
Accidental injury	2%	1%
Back Pain	2%	0%
Abnormal dreams	2%	1%
Nervousness	2%	1%
Pruritis	2%	1%

The following chart displays the adverse events occurring in at least 2% of eszopiclone treated patients with an incidence at least twice that in the placebo patients in the 6 week study:

ADR	ESZ N=209	PBO N=99
Unpleasant Taste	26%	3%
Somnolence	9%	3%
Infection	8%	3%
Dry Mouth	6%	3%
Rash	3%	1%
Viral Infection	3%	1%
Anxiety	2%	0%
Depression	2%	0%
Hallucinations	2%	0%

The following chart displays the adverse events occurring in at least 2% of eszopiclone treated patients with an incidence at least twice that in the placebo patients in the 6 month study:

ADR	ESZ N=593	PBO N=195
Unpleasant Taste	26%	6%
Infection	16%	7%
Dizziness	10%	3%
Pharyngitis	10%	5%
Somnolence	9%	3%
Back Pain	8%	3%
Dry Mouth	7%	2%
Depression	5%	2%
Anxiety	4%	2%
Arthralgia	3%	1%
Fever	2%	1%
Neck Pain	2%	1%
Peripheral Edema	2%	1%
UTI	2%	1%
Otitis Media	2%	1%

The following ADRs can reasonably be considered to be dose related:

Two Week Studies in Elderly Subject

ADR	Pbo	1 mg	2 mg
Dry Mouth	2%	2%	7%
Dizziness	2%	2%	6%
Unpleasant taste	1%	7%	12%

Six Week Study in Non-elderly Adults

ADR	Pbo	2 mg	3 mg
Infection	3%	5%	10%
Dry Mouth	3%	5%	7%
Hallucinations	0%	1%	3%
Libido Decreased	0%	0%	3%
Unpleasant taste	3%	17%	34%

Vital Signs and EKG findings

There were small mean decreases in systolic blood pressure (mean decrease of 5-6 mm Hg at 3 mg [N=123] vs essentially no change from baseline in placebo patients [N=124]) measured close to Tmax. There appears to have been no presentation of the proportion of patients by treatment group who met outlier criteria for vital signs. There were no orthostatic vital sign data submitted.

There were no important mean changes in any EKG parameters measured at approximate Tmax in 57 patients treated with 3 mg in a Phase 1 study. There also appears to have been no presentation of the proportion of patients who met outlier criteria for EKG intervals.

Laboratory tests

There were no important between-treatment mean changes in routine laboratory tests in the 6 month controlled trial, nor were there any important between-treatment differences in the proportion of patients who met outlier criteria for routine laboratory tests in this study.

Next Day Effects

The sponsor performed two formal cross-over studies (each with N=12), one in healthy volunteers, one in patients with chronic insomnia, in which patients received one night each of Estorra 2 mg, 3 mg, flurazepam 30 mg, and placebo. Each patient was tested with a battery of computerized cognitive tests that ostensibly assessed numerous domains of functioning (e.g., various measures of attention, speed of recognition, responses, etc.) at both 9.5 and 12 hours after dosing. In general, there were numerous decrements in functioning on drug (some dose related) compared to placebo, though few reached formal statistical significance (see Dr. Brugge's review, appendix, Tables VIIA1-VIIA12, pages 202-214).

Formal testing of next day effects in chronically treated patients was not done.

Withdrawal effects

The sponsor presented withdrawal adverse events for three two studies: Study 046, the 6 week trial in non-elderly adults, Study 048, a 2 week trial in elderly patients, and Study 049, the 6 month trial. For the latter study, as Dr. Brugge notes, the sponsor reported spontaneously reported adverse events within the 2 weeks after drug discontinuation; therefore, this cannot be considered an adequate assessment of potential withdrawal effects.

In Study 046, the sponsor assessed various sleep parameters throughout the treatment period and on the first and second nights after drug discontinuation. In

general, patients withdrawn from drug demonstrated a worsening on these measures compared to their last on-study measurements, as well as a worsening on these measures compared to their pre-study baseline (this latter is usually considered as the definition of "rebound"). Some of these changes, both within-treatment as well as drug-placebo differences were statistically significant, more commonly on the first post-discontinuation night. These changes were resolving by the second post-discontinuation night.

Adverse events after drug discontinuation were those reported the day after drug discontinuation if the patient completed the study or within 48 hours after early discontinuation. Only Abnormal Dreams (0%, 0%, 2% in the placebo, 2 mg, and 3 mg groups, respectively) appeared to increase with dose.

In Study 048, there also appeared to be a worsening on several sleep parameters on the first night after drug discontinuation compared to the last on-treatment night, but in general the post-treatment values were about the same as those at baseline. Although several adverse events occurred at a greater incidence in the 2 mg group compared to placebo within the first 1-2 days after treatment discontinuation, any specific event appeared to have occurred in no more than a few patients.

Other Potential Safety Issues

As Dr. Brugge notes, there appears to be an increased incidence of "Infection" on drug compared to placebo, but the sponsor has included under this preferred term only a restricted set of verbatim terms (e.g., the sponsor did not include pharyngitis, bronchitis, etc. in their incidence calculations). While it is not obvious why there should be an increase in the incidence of various kinds of infection on drug compared to placebo, we cannot ignore the finding, if it is one.

Further, there also appears to be an increased incidence of "Accidental injury" on drug compared to placebo, but, as in the case of "Infection", it is not clear that the sponsor has included all possibly relevant verbatim terms in this calculation ("accidental injury" is a preferred term under which sponsors often do not subsume all potentially relevant verbatim terms, in my experience).

Carcinogenicity

As noted above, the issue of carcinogenicity has been prominent in the development of this drug. The division had previously informed RPR that the

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In this application, the sponsor has submitted the carcinogenicity studies previously performed with zopiclone, as well as additional studies they have

performed with eszopiclone itself. These latter studies include two year studies in mice and rats, as well as a p53 study in mice (eszopiclone and a primary metabolite, S-desmethylzopiclone, are genotoxic). As Drs. Atrakchi and Rosloff note, all of the studies done with eszopiclone itself are negative. The two year mouse study, however, is considered technically inadequate, because an MTD was not reached; in this study, though, exposure to S-zopiclone was greater than that in the study with the racemate. The two year rat study reached an MTD, but the exposures to s-zopiclone in this study were less than those achieved in the rat study with the racemate.

As noted, all of the tumor findings were seen only in the studies with the racemate.

Four tumor types were seen: fibromas and sarcomas in male mice, pulmonary adenomas and adenocarcinomas in female mice, mammary adenocarcinomas in female rats, and thyroid follicular cell carcinomas in male rats. The sponsor has provided arguments to support their conclusions that these tumors are not relevant for people.

Regarding the fibromas and sarcomas in male mice, the sponsor argues that the increase in these tumors was secondary to aggression in mice that were group-housed (fighting resulted in the production of encrustations leading to tumors). Studies done in animals caged individually showed no such tumors. Both Drs. Rosloff and Atrakchi agree that the sponsor's explanation is acceptable.

Regarding the thyroid follicular cell carcinomas in male rats, the sponsor argues that these tumors are a result of increased circulating TSH that is related to a decrease in circulating thyroid hormone that is itself secondary to induction of hepatic metabolizing enzymes. This is a commonly proposed mechanism presumed to underlie this tumor type in animals, and it is also generally agreed that this mechanism is irrelevant for humans. Both Drs. Atrakchi and Rosloff agree that this argument reasonably supports the conclusion that this tumor type is not relevant for humans.

Regarding the pulmonary tumors in female mice, the relevant incidences are given below (taken from Dr. Rosloff's memo of 2/19/04):

	Control 1	Control 2	1 mg/kg	10 mg/kg	100 mg/kg
Adenoma	9.6%	7.7%	9.6%	5.7%	19.2%
Carcinoma	0%	0%	1.9%	0%	3.8%
Ad or Ca	9.6%	7.7%	11.5%	5.7%	23.1%

The trend test for the combination of adenomas and carcinomas is statistically significant, although the tests for adenomas and carcinomas individually were not.

The incidence of adenomas in the high dose group was outside the range of the historical control for the lab (upper limit 6.8%), but, as Dr. Rosloff notes, this may be misleading; in this study, the sponsor performed 10 sections per animal, while in the studies that constitute the historical control, the more typical 2-3 sections/organ were performed. Further, the incidences given in the table above were obtained from a Pathology Working Group (PWG), which diagnosed fewer tumors than the lab's pathologists (suggesting that historical control values, had they been determined by the PWG, might have been different than those quoted).

In addition, there were no early onset of tumors, and, as noted, there were no such tumors seen in the study of s-zopiclone, in which exposures at the high dose were about 10 times those achieved in this study of the racemate (although, as Dr. Rosloff notes, this study used a different strain and dosing regimen).

Regarding the mammary adenocarcinomas in female rats, the following chart, again taken from Dr. Rosloff's memo, presents the relevant incidences:

Control 1	Control 2	1 mg/kg	10 mg/kg	100 mg/kg
8%	22%	18%	30%	36%

The incidence of these tumors in the high dose group was statistically significantly greater than that in the combined control group, and the incidences in the mid and high dose groups were greater than the upper limit (18.6%) of the historical control from this lab.

The sponsor argues that these tumors are the result of a state of drug-induced early senescence in these animals, with attendant constant estrogen secretion (specifically, reproductive senescence is presumably initiated by a blockade of LH surges, which results in persistent estrus and constant estrogen secretion; this mechanism does not occur in humans). However, as both Dr. Rosloff and Atrakchi conclude, this mechanism is not well supported by the sponsor's argument for the following reasons:

They have not adequately documented that zopiclone produces consistent LH blockade.

While some drugs (e.g., atrazine) do produce LH blockade and early senescence and mammary tumors, other drugs (e.g., zaleplon and zolpidem) produce LH blockade but are not associated with mammary tumors.

While treatment with the racemate did result in early senescence (diagnosed histopathologically) in rats, treatment with s-zopiclone resulted in an even greater degree of early senescence, but was not associated with mammary tumor formation.

Other mechanisms (as Dr. Rosloff suggests, for example, changes in estrogen levels secondary to actions other than LH blockade) could account for similar results, but were not investigated.

Although no mammary tumors were seen in the study with eszopiclone, the exposures to s-zopiclone in that study were about 50% of those seen in the study of the racemate. Still, the exposure at the high dose in the s-zopiclone study is about 80 times that at the proposed human dose. However, assuming linearity, the exposure to s-zopiclone at the dose associated with a numerical, but not a statistically significant, increase in tumor incidence in the racemate study (10 mg/kg dose) is about 16 times that achieved in the human (in particular, if the margin is 80 fold in the high dose s-zopiclone study, and this exposure is 50% of that seen in the high dose group in the racemate study, the exposure margin to s-zopiclone in the racemate study would be 160 fold at the 100 mg/kg dose. This implies that the exposure margin at the 10 mg/kg dose would be about 1/10 of this, or 16 fold).

As noted by the clinical review team, the number of tumors seen in the data base is unclear. It appears that the number of tumors (benign and/or malignant) diagnosed in either the double-blind portion of Study 049 (the 6 month controlled trial) or the open-label experience is not clearly reported. It appears, from my reading of the reviews, that a total of 7 patients were diagnosed with tumors in the open-label experience, but anywhere from 16-24 patients were diagnosed with tumors in the 593 drug treated patients during the controlled portion of Study 049, compared to 0/195 placebo patients. The sponsor has not provided a comprehensive report of the tumor incidence in their database, nor have they provided sufficient details about the individual cases for the team to be able to adequately assess this issue (clearly, the team is not even able to unambiguously determine the number of such potential cases). Dr. Boehm has reviewed the sponsor's report of post-marketing cases for zopiclone (based on PSURs and PEM data); while he concludes that there is no affirmative signal, he also concludes that these data are not adequate to assess the risk for cancer.

Other issues

DMETS has concluded that the sponsor should not be permitted to use the brand name Estorra, because of the similarity to Estrace, a treatment for moderate to severe vasomotor symptoms associated with menopause, marketed as a tablet and a vaginal cream. Both drugs are available in a 2 mg strength. Their

assessment reveals a fairly striking similarity between the appearance of both names when written in script.

COMMENTS

The sponsor has submitted the results of five randomized controlled trials in patients with chronic insomnia, as well as one randomized trial in normal volunteers in a model of transient insomnia. These trials document highly significant between-treatment differences for all doses (2 and 3 mg in non-elderly adults and 1 and 2 mg in the elderly) on their respective primary outcomes, either objective or subjective measures of sleep latency. Both 2 and 3 mgs also have shown significant differences from placebo on measures of sleep maintenance (either objective WASO or subjective total sleep time) in the non-elderly, and 2 mg has been shown to result in a significant drug-placebo difference on sleep maintenance in the elderly. In the non-elderly, the 3 mg dose appears to provide a superior effect (as measured by numerical advantage over the 2 mg dose) for both sleep latency and maintenance.

I believe that the sponsor has submitted substantial evidence of effectiveness of Estorra as a hypnotic that can effect sleep latency and maintenance. I also agree with Dr. Andreason that Study 045, a 6 period cross-over study, while also highly "positive" by protocol, may not be considered a critical study because the design is not typically relied upon as appropriate for a trial contributing to a finding of substantial evidence of effectiveness.

Dr. Brugge raises a number of objections to the sponsor's conclusion that effectiveness has been demonstrated. I agree with Dr. Andreason that effectiveness has been demonstrated, and find most of Dr. Brugge's objections less than compelling (in particular, for example, I do not find the mistaken administration of "stock solution" to 6-8% of patients in Study 026 particularly problematic, given the overwhelming statistical significance seen in this, and all other studies). I do agree, however, that the large incidence of "Unpleasant taste", especially in the higher dose group, is potentially problematic with regard to the maintenance of the blind. Although I believe that this has not irreparably damaged the studies (for example, in some studies the incidence of the ADR was relatively low in the drug group), I also believe that the sponsor should be asked to address this question. For example, they might perform an exploratory analysis of the patients who did not report this ADR; while this would be, of course, an analysis of non-randomized patients, subject to all of the expected problems, the results might be of interest. Further, a fuller explanation of the time course of this ADR might be helpful (for example, if the unpleasant taste resolved soon after treatment initiation, it might be considered less likely that this would have an effect further out in time during the trial).

The sponsor has also accrued sufficient experience in the relevant population at the relevant doses with which to adequately assess the safety in use of Estorra.

As far as I can tell, given the data as presented, there appears to be no obvious finding that would, all other things being equal, preclude approval.

However, I believe the sponsor has not provided sufficient details of some adverse events in order to allow us to conclude that the safety data are adequate for approval at this time.

Specifically, the sponsor has not provided an adequate assessment of the adverse events "Infection" and "Accidental Injury". In each case, preliminary examination suggests an incidence greater than in the placebo group, but the sponsor has not adequately identified all events that could potentially be classified in these categories. Dr. Brugge describes in detail how this is true for "Infection", and I believe it is equally true for "Accidental injury". In particular, a detailed examination of the verbatim terms that might reasonably be considered appropriate to subsume under this preferred term (e.g., bruising, laceration, etc.) has, in other settings, given a clue to drug-related hypotensive related events. This is particularly important in this case, given that the sponsor did not provide any orthostatic vital sign data. I recommend that the sponsor examine their database for all verbatim terms that could reasonably be related to these two preferred terms, and perform a detailed analysis of any drug (and dose) related events.

Further, as noted, the sponsor has not provided any orthostatic vital sign data. I believe they should, or justify why this should not be necessary. While it is true that patients should take the drug immediately before going to sleep, it is certainly possible that this will not happen uniformly were the drug to be widely available.

Of course, the review team is particularly concerned about the apparent increased incidence of neoplasia in the 6 month controlled trial. The cases are not adequately characterized, and the team cannot even be certain of the total number of such cases. I agree that the sponsor should perform a comprehensive examination of these cases, and provide us with a coherent analysis of the issue of tumor (benign and malignant) occurrence in the controlled trial database. Until this issue has been further clarified, it is difficult to state whether or not this is an issue of concern (while I admit that it is difficult to imagine that Estorra has either caused or promoted tumor formation, especially of multiple types as reported, in this extremely short time frame, I still believe that the sponsor has not adequately addressed this issue, an issue, as the review team notes, about which we had expressed considerable concern prior to the submission of the application). This "finding", however, would not preclude the issuance of an Approvable letter.

I also agree with DMETS' conclusion that the trade name Estorra has the potential to result in medication errors related to its similarity in appearance to Estrace, which also is available a 2 mg dosage strength. In my view, it is more

appropriate to prevent these errors from occurring by changing the name prior to marketing rather than trying to deal with the errors after the fact, an outcome that is often difficult to achieve, and the success of which is equally difficult to assess. Finally, however, we are left with the issue of the carcinogenicity findings in animals. I agree with the pharmacology review team that the skin and thyroid tumors are dissmissable.

However, the pulmonary tumors in the female mouse are not as easily ignorable. As Drs. Atrakchi and Rosloff note, the combined incidence of adenomas and carcinomas is statistically significantly greater in the high dose group than in the placebo group. Dr. Rosloff concludes that the signal for drug induced tumors is real but small, given that it only occurred in one sex of one species, and that there was no evidence of early onset of tumor formation. Further, the tumor was only seen in the study of the racemate, and although the study of the s-isomer did not reach an MTD, the exposure to the s-isomer in that study at the high dose was about 12 times the exposure to the s-isomer at the high dose in the racemate study. I agree that the signal for this tumor type is small, although, as Dr. Rosloff notes, it is not negative.

The female rat mammary tumors pose a bigger problem, in my view.

As noted, the incidence of tumors in the high dose group is significantly greater than in the combined control groups (combining the control groups is, in my view, the appropriate maneuver when considering the control rate). As Drs. Rosloff and Atrakchi both clearly describe, the sponsor has not adequately documented that their proposed mechanism of tumor formation (early senescence caused by blockade of LH surges resulting in constant exposure to estrogen) is responsible for the occurrence of these tumors (had they been able to establish this mechanism, it would likely have convinced us that the tumors were irrelevant for people). I completely agree with the team that this mechanism has not been established.

The question, then, is whether or not the tumor signal is of concern for patients.

The tumor was not seen in the study of the s-isomer, and the margin between the exposure to the s-isomer in that study and the recommended human dose is about 80. This margin would be important if the tumor formation was attributable to a non-genotoxic mechanism, as Dr. Rosloff suggests it might be.

However, I have discussed this issue with Dr. Rosloff, and he acknowledges that we do not have strong evidence that the tumor formation is as the result of a non-genotoxic mechanism. Further, as I described earlier, making some apparently reasonable assumptions about dose linearity, the exposure to the s-isomer in the racemate (tumor positive) study at the 10 mg/kg/day dose, not, in my view, a true NOEL, would be expected to be only about 16 times greater than the exposure in the human at the recommended dose.

Further, we know the drug and its major metabolite (the desmethylzopiclone) are clastogenic, so it is at least reasonable to suggest that the tumor formation might be via a genotoxic mechanism.

I am aware that the p53 mouse study was negative; this assay is presumed to be sensitive to genotoxic compounds, but based on my discussions with Drs. Rosloff and Atrakchi, it seems that this assertion is not particularly well supported by evidence. In summary, the arguments in favor of concluding that these tumors pose no risk for humans is that they did not appear in the study of the s-isomer, the safety margin at the highest dose in that study is about 80, and the p53 study was negative. On the other hand, the margin at the NOEL in the study in which the tumor did occur is (or is expected to be) on the order of about 16, we have no good evidence (from the study itself) that the mechanism of tumor formation is tumor promotion, the drug and its major metabolite are clastogenic so it is reasonable to raise the possibility that the mechanism of tumor formation is, in fact genotoxic (in which case the notion of a safety margin is presumably much less relevant), and the evidence is weak that the p53 is adequately sensitive to genotoxic carcinogens.

I conclude from this that the finding is not ignorable, and can be considered of concern for people. While, as stated, there is much to support the view that this is of no concern clinically, I believe that the arguments in favor of considering this a potential signal of concern are more powerful. I acknowledge that this is somewhat conservative, but it seems appropriate in my view.

Of course, the question then becomes whether or not the signal is sufficient to preclude approval.

In considering this question, we must consider the strength of the signal, the indication for which it is being proposed, and, even, perhaps, the risks of other available treatments.

Considering the latter point first, Dr. Rosloff notes that the labels for the two most recently approved hypnotics, zolpidem and zaleplon, mention tumor findings, albeit not strong ones. I would only add that in both cases the Agency seemed to have determined that these findings were not relevant for humans. In particular, although he states that there is a cryptic statement about the relationship between renal tumors and zolpidem, my reading of the label suggests that the Agency considered this not to be a "real" finding at all.

I think that the mouse tumors (and, to a lesser degree) the rat pulmonary findings, are true findings, and pose at least a potential risk for humans, for the reasons given above. Given this conclusion, it is, of course, impossible to predict how significant a risk (if any) this poses for humans, but it would appear small. I would argue, however, that a risk of this sort (carcinoma), in the setting of

recently approved drugs without such a potential risk, for the indication insomnia, for a treatment with no evidence of a benefit of any sort compared to other available treatments, is too great a risk to justify approval. For this reason, I recommend that the application be considered Not Approvable, and the attached Not Approvable letter be issued.

Because there is however, also a reasonable argument to be made for considering the application Approvable (this would entail, in my view, a conclusion that the animal carcinogenicity findings are not relevant and/or pose an acceptable risk to humans, conclusions with which I obviously disagree), we are forwarding a draft Approvable letter, as well as draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
2/20/04 10:56:45 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: November 7, 2003

FROM: Paul J. Andreason, M.D. 11/7/03
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Non-Approvable Action for Eszopiclone for the Treatment of Insomnia

TO: File, NDA 21-476
[Note: This memo should be filed with the January 30, 2003 original submission of these NDAs.]

1.0 BACKGROUND

Eszopiclone (Estorra®) is the *S*-enantiomer of zopiclone. Zopiclone is marketed in several non-US countries as a hypnotic, [illegible] appeared to be a strong signal of animal carcinogenicity. This pre-clinical signal consisted of skin, thyroid, lung and mammary tumors. Racemic (RS)-zopiclone was originally developed by Rhône-Poulenc Rorer (RPR) and is currently marketed by RPR in 85 countries, including Great Britain, France, Germany, Canada, Norway, Sweden, and Japan under the trade names Amoban®, Datolan®, Datovane®, Foltran®, Imovane®, Limovane®, Siaten®, Ximovan®, and Zimovane®.

It is my understanding that the original approval outside of the US was based on the judgment that the animal findings were irrelevant to humans and that zopiclone was not mutagenic. Recently, however, eszopiclone mutagenicity studies were positive and S-desmethyl zopiclone, a major metabolite of eszopiclone was found to be clastogenic. The relevance of the animal findings to humans in zopiclone remains controversial. The Division's position has been that there are multiple effective hypnotics on the market that do not have animal cancer signals and we need not approve one that does.

I note that the review of this NDA was difficult for many of the review disciplines including the clinical reviewer. Some critical items were missing at filing that the sponsor provided very close to the filing decision deadline. In some cases, items from the 75-day letter arrived very late in the review cycle. One of these was the post-marketing analysis of cancer cases for zopiclone.

The application itself was difficult to navigate. The original application was provided in what I can only describe as a draft format with multiple errata documents appended to it. These did not appear to be trivial changes at the time of filing. These errata documents were merely attached to the original submission and were neither incorporated nor

hyperlinked into the electronic document. As a condition for filing we required the sponsor to replace the incorrect sections in their submission. The finished filable submission arrived to us within a few days of the filing date. In the end, time ran out on the review cycle and an action was due. This is the reason that we are still not certain as to the number of reports of neoplasia in study 190-049; we did not have time to clarify this with the company given the multiple problems leading up to the action deadline.

2.0 CHEMISTRY

The Chemistry Team has issued a CMC deficiency letter and judged that the submission was approvable from a chemistry standpoint.

3.0 PHARMACOLOGY

The Pharmacology Toxicology reviewer, Dr Atrachi, recommends that eszopiclone not be approved from a pre-clinical standpoint. She states that the pre-clinical profile for for RS-zopiclone and S-zopiclone leaves incompletely explained mammary tumors in rats, positive clastogenic responses in *in vitro* mammalian assays for RS-zopiclone, S-zopiclone, and the active metabolite S-desmethyl zopiclone, and marked reproductive toxicity and adverse effects on male and female rat fertility. She states that the results to date from the mechanistic studies only partially support the theory that the mammary gland tumors were induced as a result of early onset reproductive senescence. Her conclusion is supported by the fact that zaleplon and zolpidem, both GABA agonists from the same drug class cause estrus cycle disturbances, but neither drug induced mammary tumors or any relevant tumors in two-year carcinogenicity studies.

4.0 BIOPHARMACEUTICS

The OCPB review Team found that there was sufficient data to take an approvable action from an OCPB standpoint. Their recommendations for labeling and recommendations to the sponsor are outlined in their review.

5.0 CLINICAL DATA

5.1 Efficacy Data

The Sponsor makes a claim for efficacy in for both transient and chronic insomnia. They support the claim for chronic insomnia based on the results of five studies. Two of the five pivotal studies were performed in elderly patients (190-047, 190-048) while the remaining three pivotal chronic insomnia studies were performed in adults (190-045, 190-046, 190-049). Their claim for transient insomnia is based on the results of one positive study (190-026).

5.1.1 Summary of Studies of Chronic Insomnia

The design of each of the trials supporting the claim for chronic insomnia in adults follows in tabular form:

Protocol/ Study Population	Study Design	Treatment Groups (oral tablet unless otherwise specified)	N(Completers) (% of ITT Safety)	N (ITT Efficacy)
190-045 PSG Cross-Over Trials in Non-Elderly Adult Patients with Chronic (Primary) Insomnia				
Efficacy PSG Study Non-Elderly Adults with Chronic Insomnia	MC (7 sites), DB , 2-Day dosing per Treatment Condition/Visit, 6-Way X-over, Random., PC	2-Day Dosing: 1 mg ESZ 2 mg ESZ 2.5 mg ESZ 3 mg ESZ Placebo group	**Total:** 63 (97%)	63-64/Condition

190-046 6-Week (44 nights) PSG Parallel Group Trial in Non-Elderly Adult Patients with Chronic (Primary) Insomnia

Efficacy and Safety, PSG/Outpatient Study Non-Elderly Adults with Chronic Insomnia	MC (51 sites), MD (44 Days),DB, Parallel, Random., PC	44 Days Treatment- Last PSG visit on Treatment Day 29:		
		2 mg ESZ	97 (93%)	104
		3 mg ESZ	101 (96%)	105
		Placebo group	94 (95%)	99
			Total: 292	**Total: 308**

190-049 Long Term (6 months DB, 6 months Open Label Extension) Sleep Diary, Outpatient, Parallel Group Trial in Non-Elderly Adult Patients with Chronic (Primary) Insomnia

A Safety & Efficacy Sleep Diary/Outpatient Study Non-Elderly Adults with Chronic Insomnia	MC (69 sites), Random., PC, MD, 6-month DB- Parallel, then 6-month Open Label Extension	6-months DB Phase:	6-months DB Phase:	6-month DB Phase:
		3 mg ESZ	360 (61%)	593
		Placebo group	111 (57%)	195
			Total: 471	**Total: 788**
		6-months Open Label Extension Phase (OL):	6-months OL ESZ: 382 (81%)	6-months OL ESZ: 471
		3 mg ESZ	DB & OL ESZ: 12 mo. ESZ: 296 6 mo. Placebo & 6 mo ESZ: 86	DB & OL ESZ: 12 mo. ESZ: 360 6 mo. Placebo & 6 mo. ESZ: 111

MC- multi-center, MD- multiple dose, PC- placebo controlled, OL- open label, DB- double blinded, Parallel- Parallel Group Design, ESZ-eszopiclone

Study 190-045 was a double-blind six-treatment cross-over study. Though the Division views crossover studies as supportive, we do not usually view them as pivotal studies in sleep trials. These are usually considered as part of the phase II dose finding portion of the development program. This is because sleep parameters measured later in the study will be improved over baseline merely due to the better sleep hygiene practices that are enforced by the course of the study. Likewise, as Dr Brugge notes, there is an unpleasant taste associated with eszopiclone that is reported in a dose dependent fashion. Given the nature of the crossover study, this potential source of unblinding will have a greater chance of biasing a crossover study where the taste of one treatment may be compared against that of another.

Nonetheless, in study 190-045 the sponsor's primary efficacy variable was the objective (polysomnographically measured), average 2-night value of the latency to persistent sleep (LPS). They claim a "key secondary variable" of Sleep Efficiency (total time slept /time in bed). Both items were significantly better than placebo at all doses. Sleep parameters usually improve in all groups over the course of the study.

Study 190-045 Latency to Persistent Sleep						
		Eszopiclone				
Objective Latency to Persistent Sleep	**Placebo**	**1.0-mg**	**2.0-mg**	**2.5-mg**	**3.0-mg**	**Zolpidem 10-mg**
N	63	63	63	65	64	64
Mean	37.8	25.2	20.1	18.6	18.3	16.6
Median	29.0	16.8	15.5	13.8	13.1	13.1
Overall Effect			≤0.0001			
Pairwise p-Value vs Placebo		≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Key secondary variables of wake-time-after-sleep-onset (WASO) and sleep efficiency were also analyzed. Sleep efficiency was significantly improved over placebo at all doses for Eszopiclone and zolpidem. WASO was significantly better than placebo for 2.5 (p=0.02) and 3.0-mg (p-0.01) groups but not for 1.0, 2.0, or for zolpidem 10-mg.

Study 190-046 is a double-blind, parallel group 44-night study of eszopiclone at 2 and 3-mg in patients with chronic primary insomnia; however, the primary efficacy variable was PSG measurement of LPS, the last of which was on night 29. At the time points of 1, 15 and 29 days of treatment both 2 and 3-mg doses significantly separate from placebo on LPS by PSG (the primary efficacy variable.

Study 190-046 LPS by PSG			
Objective Latency to Persistent Sleep	**Placebo**	**2.0-mg**	**3.0-mg**
Entire study			
N	99	104	105
Mean (SD)	33.0 (22.6)	23.0 (24.9)	18.0 (15.7)
Median	29.0	15.5	13.1
Pairwise p-Value vs Placebo		≤0.0001	≤0.0001
Night 1			
N	96	102	105
Mean	35.2 (28)	21.4 (27.6)	17.5 (20.2)
Median	28.6	11.8	12.3
Pairwise p-Value vs Placebo		≤0.0001	≤0.0001
Night 15			
N	95	97	100
Mean	34.0 (28.0)	21.9 (21.1)	19.5 (19.6)
Median	27.0	15.5	13.8
Pairwise p-Value vs Placebo		≤0.0001	≤0.0001
Night 29			
N	95	98	100
Mean	30.2 (28.2)	24.0 (35.8)	18.1 (26.1)
Median	20.5	12.9	11.5
Pairwise p-Value vs Placebo		0.0009	≤0.0001
ANOVA on rank transformed data using MIXED procedure			

The key secondary variables of WASO and sleep efficiency were not uniformly positive throughout all time points in the 3-mg group. Though the 3-mg group was positive at all time points for sleep efficacy, it failed only at night 15 for WASO. WASO was only positive on night 1 in the 2-mg group. Sleep efficiency failed at night 15 but was positive at other time points.

Study 190-049 was a 6-month double-blind, placebo controlled study of adults with chronic primary insomnia. The primary efficacy variable was subjective sleep latency (often referred to as time-to-sleep-onset [TSO] in the literature). 593 patients were assigned to the eszopiclone treatment groups and 195 to the placebo group. According to table VIC19 in the appendix of Dr. Brugge's review, 69% of the eszopiclone treated patients received at least 5-months of double blind therapy. The sponsor averaged months 1-3 and 4-6 as well as each month individually. All of these analyses of mean TSO were significantly less than placebo with the mean effect size varying from 14-20 minutes of improvement ($p \leq 0.0001$). The key secondary variable of total sleep time was also positive at all time points ($p \leq 0.0001$).

Elderly Patients with Chronic Insomnia

The following table outlines the design and enrollment characteristics of the two controlled studies of elderly patients with chronic primary insomnia.

Chronic Insomnia Trials in Elderly Adults

Protocol No and Study	Study Design	Treatment Groups	N- Completers (% of ITT Efficacy Population)	N- ITT Efficacy
190-047-2-Week PSG Efficacy and Safety Study Elderly Adults (65-86 yo) with Chronic Insomnia	MC (48 US sites, 2 Canada sites), DB,2-week MD, Parallel Group, PC	1.5 mg ESZ (aborted)	Aborted @ n=28	
		2 mg ESZ	133 (98%)	136
		Placebo group	122 (95%)	128
			Total: 283	**Total:264**
190-048-2-Week Sleep Diary Efficacy and Safety Study Elderly Adults (64-85 yo) with Chronic Insomnia	MC (32 sites), DB, 6-week MD, Parallel Group, PC	1.0 mg ESZ	67 (91%)	72
		2 mg ESZ	70 (89%)	79
		Placebo	73 (90%)	80
			Total: 210	**Total: 231**

Study 190-047 was a study of 292 65-85 year-old patients with chronic insomnia. It was a multi-center double blind, placebo controlled, fixed dose parallel group, two-week study that used PSG as a primary efficacy measure. The Sponsor analyzed two co-primary PSG variables- median LPS and median Sleep Efficiency of the 2-mg group. Both were significantly better than placebo at nights 1 and 14 ($p \leq 0.0001$). They also designated WASO in the 2-mg group as a key secondary variable that was significantly less than placebo.

Study 190-048 was a study of 231 65-85 year-old patients with chronic insomnia. It was a multi-center double blind, placebo controlled, fixed dose parallel group, two-week study that used sleep diaries administered via an interactive voice response system (IVRS) as a primary efficacy measure. The Sponsor analyzed two co-primary sleep diary variables- median subjective sleep latency and median sleep efficiency of the 2-mg group. Both were significantly better than placebo at nights 1 and 14 ($p \leq 0.001$). They also analyzed a key secondary variable, subjective total sleep time in the 2-mg group, that separated from placebo at both nights 1 and 14.

5.1.2 Summary of Studies of Transient Insomnia

Study 190-026 of transient insomnia used the test model of healthy volunteers during their first night in the sleep lab. In Dr Brugge's review she was concerned about the sponsor using a post-study blinded committee to determine which patients could be considered for evaluation. She was mistaken in her belief that this applied to the analysis of the primary efficacy variable. This post-study exclusion of patients applied to their analysis of the DSST, a safety measure. Though the use of such a board is questionable for the DSST analysis, the sponsor did in fact analyze the ITT patient population in the efficacy analysis.

Tabular results of this study follow:

Study#	Objective Latency to Persistent Sleep[LPS] (minutes)	Placebo	Esopiclone	
			3.0mg	3.5 mg
190-026	N	98	98*	96
	Mean	17.90	9.10	6.62
	Median	12.5	5.5	5.0
	Overall treatment effect**		≤0.0001	
	Pairwise p-value vs. placebo		≤0.0001	≤0.0001

*One subject from 3.0mg arm did not have analyzable objective PSG data but was included in the efficacy analysis for subjective measures.

* *The overall treatment effect and pairwise comparisons were tested using an ANOVA model on rank-transformed data with effects for site and treatment, using only subjects in the placebo, Esopiclone 3.0 mg, and Esopiclone 3.5 mg groups.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor presents 5 studies in support of the efficacy of zopiclone in the treatment of chronic insomnia. All patients had placebo exposure either through a placebo control in the cross-over study or a placebo run-in. This presents a setting where the unpleasant taste of the zopiclone can be detected and compared. Had there been no placebo run-in in the parallel group studies then the bitter taste could still be considered behind the blind, because patients would be less informed as to if it were the pill or the active ingredient in the pill that was responsible for the taste. Generally speaking, unblinding is a common practical problem in clinical trials. It is unfortunate that the sponsor did not control for the unpleasant taste in their formulation as the Division had suggested.

The review of the studies from the Division of Biometrics and Statistics confirmed the results of the sponsor's analysis. Given the weight of evidence, I conclude that eszopiclone is effective in the treatment of both transient and chronic insomnia.

5.2 Safety

Clinical Exploration of Pre-clinical Carcinogenicity Signal

The unresolved clinical safety concern that I have about eszopiclone has its root in the preclinical carcinogenicity findings discussed above in section 3. These preclinical carcinogenicity findings with the racemate kept zopiclone from the market in the US. The sponsor had not included a post-marketing analysis of reports of cancer associated with zopiclone in the original NDA. In the context of the preclinical findings and as a condition for filing the NDA for eszopiclone, the Division asked the sponsor to do an analysis of the reported cases of neoplasia in post-marketing adverse event data for zopiclone. Additionally, given the 6-month double-blind treatment period it was incumbent on the clinical reviewer to look for any cancer signals in the controlled trial database as well as the extended open label experience.

The analyses of post-marketing experience of zopiclone and 6-month controlled trial data of eszopiclone are necessary for the work-up of this drug. The reason being that even though this work-up does not offer mitigation for preclinical findings that are viewed as positive, these analyses if positive for a human cancer signal would confirm the concerns of the preclinical reviewer, even if those concerns were ambivalent.

The review of the spontaneous adverse event reports for racemic zopiclone was performed by Jerry Boehm, MD of the Safety Team. He stated that the presented data did not provide evidence for an increased risk of cancer in patients taking zopiclone, but that this post marketing information was not helpful in ruling out a contribution zopiclone to a potential cause for cancer.

Dr. Brugge's review of the spontaneously reported adverse events in the 6-month placebo controlled study (190-049) revealed that we need clarifying information. Due to inconsistencies in the tables, Dr. Brugge is unable to tell if there are 16 or 24 line listing reports of "neoplasia" in the 593 eszopiclone treated patients. There are 0/195 reports of neoplasia for the placebo treated patients in 190-049. It is difficult for me to gain a sense of perspective on these reports. Many seem benign from their verbatim terms but why they were coded as neoplasia is a mystery without an explanation from the sponsor. The lack of further explanation might lead one to believe that nothing of concern occurred; however, there are at least three cases that seem to deserve more than the perfunctory description that they were given.

One case (S0450024) which, by its description seems to be a progressing work-up to rule out a diagnosis of disseminated cancer, appears lost to follow-up after she drops out of the study because of her findings of nodules and neoplasia. This is not reported as a serious adverse event even though the reason for her discontinuation is coded as "neoplasia". Another event coded as Breast Neoplasm was reported in subject 0406001, a 57 year old Caucasian female with no history of medical conditions who experienced a "lump" in her left breast after approximately 1 ½ months of double-blind treatment. It was considered "benign," presumably based on ultrasound and mammography that were conducted, but the results were not described. The course of her breast lump over time were not described yet study drug was discontinued upon discovery of the "lump". Neoplasm was reported in subject 0421004, a 62 year old female with no medical problems at screening who had a "nodule in throat" after approximately 5 months of double-blind treatment. This nodule was described as being resolved 10 days after cessation of treatment. The narrative provides no other information (e.g. if any diagnostic tests were conducted). Though these are coded as neoplasm and though they lead to dropout, no detail is provided and they were never coded or reported as "serious" by the sponsor at any time during the course of the studies.

The sponsor did not seem to note the inter-group discrepancy in the number of spontaneous adverse event reports of neoplasia and perhaps consequently provided no explanation for the imbalance in their occurrence in the eszopiclone treated patients. On the other hand, I note that the entry criteria specifically restricted patients with an increased risk for breast, lung, or thyroid cancer unless they had a negative thyroid scan, chest X-ray, or mammogram within a year of the study's start. It appears from this exclusion criterion that the sponsor was aware of the animal cancer signal and made plans to limit the number of spurious cases of cancer that might crop up. Therefore if carcinoma is confirmed in any of these adverse event reports of neoplasia, then they can not be viewed in the same way we might usually look at background rates of neoplasia in clinical trials.

I do not say that these cases represent a human signal for cancer in this data, but in the end, I believe that all of these cases need to be thoroughly explained prior to considering this drug for approval given the pre-clinical findings of thyroid, mammary, skin, and lung tumors with zopiclone.

Safety Concerns related to Drug Class

Eszopiclone possesses the expected adverse event profile of the other hypnotics with comparable plasma half-lives. Dr. Brugge addresses these in her review. These included but are not limited to

hallucinations, amnesia, difficulty concentrating, memory impairment, depression, somnolence, and accidental injury. Of note, Dr. Brugge did not find any report of seizure or drug dependence.

Other Safety Concerns Raised by Dr. Brugge
Dr. Brugge raises concerns about the increased incidence of thyroid abnormalities, increased incidence of reports of infection, and differences in mean platelet counts in some of the short term controlled trial data. It is not clear to me what these findings may represent, but given the data from the 6-month controlled trial, it appears that if there is a drug effect on these parameters in the short term, then it seems to disappear or be of no clinical significance. Though the group difference in platelets remains in the long-term study, the eszopiclone patients do not have a mean decrease in their values, but the placebo group has a mean increase. There are no serious adverse events that could be attributed to decreased platelets.

6.0 WORLD LITERATURE
The sponsor performed a review of the world literature for eszopiclone and zopiclone. Our review of the zopiclone literature provided by the sponsor focused on potential carcinogenicity in humans. There are no other outstanding safety concerns with either zopiclone or eszopiclone besides carcinogenicity and clastogenicity that are not expected from the drug class as a whole.

7.0 FOREIGN REGULATORY ACTIONS
I am not aware of any foreign regulatory actions regarding the use of eszopiclone. Zopiclone is marketed in 85 countries by RPR. To my knowledge zopiclone has not been removed from any non-US market for safety reasons.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING
We decided not to take this drug to the PDAC; however, the Pharmacology Toxicology Team did take this drug to the Executive CAC for review. This is outlined in the Pharmacology/Toxicology review.

9.0 NON-APPROVAL LETTER
A non-approval letter acknowledging our decision is attached to the package.

10.0 CONCLUSIONS AND RECOMMENDATIONS
Though zopiclone appears to be effective in the treatment of insomnia, its safe long-term use remains a point of as yet unresolved concern. I recommend that the Division issue a not-approved action for NDA 21-476 from a clinical point of view. The reasons for this action are:

1. There appears to be a disproportionate number of reports of adverse events of neoplasia in the long-term double blind study of eszopiclone in patient with chronic insomnia (190-049). We are confused on the count of reports. Depending on the tables we consult there are somewhere between 16 and 24 reports of neoplasia in the 593 eszopiclone treated patients and 0/195 reports in the placebo group. Please clarify the actual numbers of reports of neoplasm in study 190-049. We recognize from the verbatim terms that many of these reports may have been improperly coded; however, in the absence of the patient data or a clearer explanation, we can not make that assumption. We are particularly curious about three cases:
    a. Subject 0450024- by your description, this patient seems to be progressing steadily in a work up for disseminated cancer and then appears lost to follow-up after she drops out

of the study. This case was not reported as a serious adverse event even though the reason for her discontinuation is coded as "neoplasia".

b. Subject 0406001- dropped out of the study for an adverse event coded as Breast Neoplasm. The summary reports that she experienced a "lump" in her left breast after approximately 1 ½ months of double-blind treatment. It was considered benign, presumably based on ultrasound and mammography that were conducted, but the results were not described. The subsequent course of her breast lump over time was not described yet study drug was discontinued upon discovery of the lump.

c. Subject 0421004- a 62 year old female with no medical problems at screening who reported a "nodule in throat" after approximately 5 months of double-blind treatment. This nodule was described as resolving 10 days after cessation of treatment. The narrative provides no other information and she appears lost to follow-up.

We do not say that these cases represent a human signal for cancer; however, the numerical imbalance of the reports of neoplasia and case histories that these numbers represent need to be thoroughly explained prior to considering eszopiclone for approval given the pre-clinical findings of thyroid, mammary, skin, and lung tumors with zopiclone, and the as yet unresolved concern about mammary tumors, mutagenicity, and clastogenicity with eszopiclone and S-desmethyl-zopiclone.

2. There is an unresolved pre-clinical signal of mammary tumors in the rat that may be relevant to humans. The pre-clinical profile for RS-zopiclone and S-zopiclone leave incompletely explained mammary tumors in rats, positive clastogenic response in *in vitro* mammalian assays for RS-zopiclone, S-zopiclone, and the active metabolite S-desmethyl zopiclone, and marked reproductive toxicity and adverse effects on male and female rat fertility. Results to date from the mechanistic studies only partially support the theory that mammary gland tumors are induced as a result of early onset reproductive senescence. Zaleplon and zolpidem, both GABA agonists from the same drug class, cause estrus cycle disturbances, but neither drug induced mammary tumors or any relevant tumors in two-year carcinogenicity studies. The Division policy has been that there are effective hypnotics on the market without animal cancer signals and that there is no reason to approve a hypnotic with such a signal. There is no compelling evidence that eszopiclone offers anything therapeutically beyond what is offered by already marketed drugs without this potentially relevant cancer signal.

After this action is taken, this NDA is transferred to HFD-170. The entire hypnotic drug group was transferred to HFD-170 in September 2003. It was decided that HFD-120 would complete the review of this submission since the drug-group transfer occurred well into the review cycle.

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/s/

Paul Andreason
11/7/03 02:30:47 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	21-476
Sponsor:	Sepracor Inc
Drug	
Established Name:	Eszoplicone
Chemical Name:	(+)-(5S)-6-(chloropyridine-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate
Code Name:	NA
Formulation:	2 and 3 mg oral tablets
Indication:	Chronic and Transient Insomnia
Dates of Submission:	March 23, 2001
Materials Reviewed:	Original NDA 21-476 (refer to section IVA for details).
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	9/15/03

EXECUTIVE SUMMARY

The purpose of this review and summary are to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-476. The summary provides a brief overview of the Clinical review of NDA 21-323 (refer to the review for more complete and detailed clinical information and clinical recommendations).

Eszopiclone (ESZ) is the S-enantiomer of zopiclone (the racemate). Zoplicone (ZOP) is a cyclopyrrolone approved in 85 foreign countries for the market (since 1987) and is primarily prescribed as a sedative hypnotic agent. ESZ is a pyrrolopyrazine derivative of cyclopyrrolone and binds to the $GABA_A$ receptor/macromolecular complex that is believed to act as a positive allosteric modulator of the GABA receptor complex. The sponsor is seeking approval for a

Several deficiencies were found in the original submission before filing, as described in this review.

A number of clinical, preclinical and chemistry/manufacturing issues were also identified before filing of the submission, as described in this review. One major issue raised before filing of the NDA was regarding preclinical observations of potential carcinogenicity effects of zopiclone and the need for preclinical data examining these potential effects with ESZ. These issues are currently under review by the Pharmacology Toxicology Review Team. At the time of this writing, the CMC Reviewer was still waiting additional information and such as DMFs on some of the formulations used in the Phase III clinical trials.

Aside from the issues to be addressed by other reviewers, a number of Clinical issues are described in this review. From a clinical perspective, it is recommended that this NDA not be approved (and not be given an approvable status). The basis for this recommendation is summarized in Section XI with some of the major issues briefly outlined here.

One major issue was a remarkable number of events of neoplasia or related events which were primarily reported as adverse events (3 events were reported as adverse dropouts). The grand total of events was at least 17, if using a line listing of AE's for the long-term study, Study 190-049 or at least 24, if using other tables and data sources as described in this review. These events were reported in ESZ treated subjects in the long-term study, Study 190-049 (in which a total of 593 subjects were randomized to ESZ in the 6-month double-blind phase and a subset of these subjects entered in the 6- month open-label phase), while no events of neoplasia or related events were reported in placebo subjects during the six-month double-blind phase of this trial (out of a total of approximately 195 randomized placebo subjects). These observations were revealed despite stringent and atypical criteria for screening subjects and excluding subjects with a risk for neoplasia, as described in more detail in this review.

While, the sponsor provides postmarketing data on the racemic agent, zopiclone (which is data under review by the Safety Group of the Division), it is the opinion of this reviewer that if no signal for neoplasia is revealed from this data, that the results cannot be interpreted as providing evidence for an absence of an association between the development or progression of neoplasia (also consider potential effects in patients with pre-existing conditions and/or risk for neoplasia prior to treatment). However in the opinion of this reviewer the utility of examining this data to establish adequate safety is not adequate regarding the concern of neoplasia with ESZ treatment. The data are only useful, if results are positive or suggestive of a signal, as such a finding from this type of data would be quite alarming, even if the given drug were a known

carcinogen. The rationale for these conclusions and comments are provided in Section XI of this review.

Other sedative hypnotic agents already exist on the market that are effective and adequately safe in which there is no evidence or a suggestion for carcinogenic effects (or any suggestion for effects as a potential promoter for development of neoplasia).

Other safety concerns that appeared to be unique to ESZ in contrast to other a sedative hypnotic agents already on the market are also discussed in this review. One of the concerns is regarding potential endocrine-related effects as described in this review that were first raised during the pre-NDA phase of drug development, yet the sponsor had chosen to submit the NDA prior to reaching resolution with the Division on these endocrine-related issues and on the need for further study in this area (as discussed with the sponsor during pre-NDA meetings).

It is noteworthy that preclinical issues also include concerns regarding neoplasia and endocrine-related effects, which are issues under review by Pharmacology/Toxicology Reviewer.

Major concerns regarding efficacy data and the interpretation of the results as provided by the sponsor are also raised in this review. For example, a drug-related and dose-dependent association of the study drug with unpleasant taste was revealed in which approximately 10 to 30% of ESZ treated subjects were reported this adverse event compared to future none of the placebo subjects (the higher incidence in ESZ subjects is associated with a dose level of 3 mg at bedtime which is the proposed recommended dose in nonelderly adult patients). Based on these findings which were reproducible among the clinical trials, this reviewer does not consider the double-blind design of the clinical trials to be adequate (e.g. the placebo was not adequately matched to the study drug in taste). Another concern is regarding methods employed in at least some of the studies in which a subgroup of subjects identified as "evaluable" subjects for the purpose of using data from these selected subjects for the primary versus secondary analyses of efficacy measures. A number of additional problems and limitations regarding, not only the efficacy data, but also some of the safety data are also discussed in this review. One of the concerns is that the quality, accuracy, and completeness of the submission are not adequate, in the opinion of this reviewer.

Another issue is that it is not clear why events of neoplasia were not categorized as serious adverse events by the sponsor (three of the events were categorized as adverse dropouts and all others were categorized as adverse events). Furthermore, the rationale for using stringent screening methods and eligibility criteria regarding patients at risk of neoplasia in the only long-term ESZ trial conducted by the sponsor (Study 190-049) is not clear. These stringent methods are atypical for a trial intended to provide evidence of adequate long-term safety of the study drug.

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I. Introduction and Background.

This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323.

A. Indication and Proposed Direction of Use

Eszopiclone (ESZ) is the S-enantiomer of zopiclone (the racemate). Zoplicone (ZOP) is a cyclopyrrolone approved in 85 foreign countries for the market (since 1987) and is primarily prescribed as a sedative hypnotic agent. ESZ is a pyrrolopyrazine derivative of cyclopyrrolone and binds to the $GABA_A$ receptor/macromolecular complex that is believed to act as a positive allosteric modulator of the GABA receptor complex. The sponsor proposes that the drug is effective for "treatment of insomnia" ir [illegible] as in proposed labeling). The recommended dose is a [illegible] tablet at bedtime and a [illegible] tablet in the elderly and in patients with severely impaired liver function. Later sections of this review describe the proposed insomnia [illegible] and direction of use in greater detail.

The sponsor reports that ESZ shows approximately 50 times greater affinity for the $GABA_A$ receptor complex than the observed affinity of R-zopiclone isomer. Preclinical and clinical trials are reported to show that compared that at half the dose of ZOP, ESZ is at least equally effective to that of ZOP. Among the 85 foreign countries where ZOP is approved for the market the recommended dose is generally a bedtime dose of a 7.5 mg tablet, although some countries approved an additional lower dose (a 3.75 or 5 mg dose). Some countries have the 5 mg dose level as the recommended starting dose (Canada, Sweden and Norway). ZOP was first approved in 1984 in France (by Rhone-Poulenc Rorer).[1]

B. State of Armamentarium for Indication

Classes of pharmacological drug products currently approved for treatment of Chronic Insomnia disorder or for short term insomnia include several non-benzodiazepine $GABA_A$ agonists (e.g. zolpidem and zaleplon) and Estazolam.

A number of benzodiazepines and other classes of drugs are on the market, several of which are often used off-label for treatment of insomnia. Other drugs or drug classes include those that are indicated for Major Depressive disorder (e.g. Tricyclic agents such as amitriptyline and trazadone, and other drug classes), drugs indicated for Anxiety disorders, and other drugs for other indications such as, antihistamines, among others. Other marketed drugs are used for sedative hypnotic effects when conducting surgical procedures.

C. Administrative History and Related Review

1. <u>The Prefiling Phase of the NDA</u>

The following are Clinical issues raised at the Prefiling phase of this NDA:

- A number of Clinical Study Reports (CSRs) had a number of errors in which these CSRs had one or several Errata documents (provided as separate documents) in the original submission listing uncorrected errors that existed within each given CSR. The sponsor was informed of this deficiency and later responded by providing corrected CSRs for several studies in a

[1] This information is described in Section 3.H.5.2 of the sumary.pdf file of the submission.

3/25/03 amendment submission (CSRs incorporating errors listed in errata documents). Other errors were found in the CSRs, but were generally clarified or corrected.

- The majority of safety results in the ISS were provided in shift tables (the incidence of subjects in a given treatment group shifting from normal at baseline to high or low on a given safety parameter during or after treatment) and not as the incidence of outliers (the incidence of subjects with abnormal value during treatment on each clinical assessment parameter). More importantly these results, as well as descriptive statistical results for the majority of integrated studies included values obtained for days and sometimes approximately a week after treatment cessation. See section VIII for further details.
- A literature search, methods of the search, a description of the review of the literature and a publication listing on ESZ could not be found in the submission. However, the sponsor later clarified that no articles on the S-enantiomer were found in the literature. Only a brief statement regarding a review of the literature for the racemate ZOP could be found in the original submission in which no new or unexpected findings were reported as being revealed in the literature. However, the methods of the search and a complete description of a review with a publication listing showing results of the literature search could not be found. The sponsor later provided some additional information from the literature for ZOP in a 120-Day Update Submission (6/30/03 submission).
- Postmarketing data was provided as periodic safety update reports. The sponsor had not summarized the incidence of safety alerts by AE terms and did not provide a description of any unexpected findings or did not conduct specific searches for events that may be of concern (e.g. potential hormonal effects and reports of neoplasia, given the observations in preclinical trials).

A number of Chemistry/Manufacturing and Preclinical issues or deficiencies were identified, as described under Section II below.

2. The IND Phase of ESZ Development.

ESZ studies were conducted under IND 58,647. A pre-NDA meeting was held on 12/17/02 in which preclinical issues and findings of neoplasia were discussed.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or other Consultant Reviews.

The submission provides information that is currently under review by the Office of Clinical Pharmacology, Biopharmaceutical (OCPB), Pharmacology Toxicology (Preclinical), Biometrics and Chemistry Manufacturing and Controls (CMC) reviewers. Abuse liability information is also under review by CSS (Controlled Substance Staff). The NDA is also under consultative review by DSI (Division of Scientific Investigation).

So far the CMC reviewer and Preclinical Reviewers have expressed major issues and deficiencies at the prefiling meeting (e.g. need DMFs for some of the tablet formulations used in clinical trials). The CMC reviewer requested the information, but is still waiting for a response to their inquiries at the time of this writing.

The Preclinical Reviewer expressed major deficiencies in the original submission and major issues at the filing meeting that primarily focused on the issue of potential carcinogenicity or on a potential adverse effect on the risk for developing neoplasia (e.g. as a oncogenic promoter). The following briefly describes preclinical observations with the racemate, as there were no preclinical trials of ESZ that adequately addressed the potential for carcinogenicity in the submission at prefiling (e.g. the sponsor was to provide preclinical information on studies with ESZ, but the original submission did not contain this information).

Racemic zopiclone CA studies were described by the Preclinical Reviewer Dr Aisar Atkrachi (as described in the filing meeting, in personal communications with Dr. Atkrachi, and in meeting minutes, as well as in other sources, . These studies revealed the following:

- Pulmonary tumors (adenocarcinoma in one gender of mice)
- Skin tumors (in one gender in mice),
- Thyroid tumors in male rats (believed by the sponsor to be secondary to increased LFTs), but pituitary tumors were also found in rats (as previously described),
- Mammary gland tumors (in female rats),
- In vitro CA ESZ studies show some positive results for genotoxicity.

The sponsor had plans to submit preclinical study results on ESZ, sometime in the NDA review cycle. It is not clear at the time of this writing if the sponsor has provided all necessary preclinical information.

At the time of this writing the Clinical Pharmacology, Biopharmaceutical (OCPB) Reviewer has not expressed any key issues (refer to their review for details and recommendations). Proposed labeling is for 2 mg and 3 mg ESZ tablets. However, the efficacy and safety clinical trials to support proposed labeling used tablets of ESZ (e.g. 1 mg, 1.5 mg) or an oral solution formulation. The sole pivotal transient insomnia trial used an oral solution formulation. Only a few of these trials included the 2 mg or 3 mg tablet, but even those trials generally used the other tablet sizes (in mg's), as well. However, according to an 8/14/03 e-mail communication with the OCPB Reviewer, the tablet and oral solution formulations are not a concern regarding the interpretation of the clinical results in these trials (i.e. the formulations can be considered bioequivalent based on pharmacokinetic results of Phase I trials).

During the prefiling meeting, the CSS reviewer expressed concerns regarding a high incidence of subjects with a history of benzodiazepine abuse that had hallucinations with ESZ treatment compared to placebo or diazepam treatment in Study 190-016. These observations are described under Section VIIIG of this review.

The Biometric Reviewer is also reviewing efficacy data. The following are biometric-related Clinical issues described in this Clinical review (as noted by the Clinical reviewer):

- An unpleasant taste associated with ESZ treatment and as reported in over 30% of subjects in some trials and generally reported in over 10% of ESZ treatment subjects in a given trial compared to approximately less than 1% (up to approximately 3%) in placebo subjects in the trials. This observation was reported in an atypically large incidence of ESZ subjects in single dose trials, as well as in multiple dose trials and was a dose-dependent effect. The issue is an adequate double-blind to the study drug, due to an inadequate placebo tablet (no adequately matched in taste to the ESZ tablet). In the

opinion of this reviewer, one could not argue that if efficacy results were to reveal dose-dependent effects on efficacy measures, that the double-blind would then be adequate. since this drug effect on unpleasant taste was found to be dose-dependent in multiple trials

- The data from an "Evaluable" population appears to have been analyzed for primary and key secondary analyses, at least for some trials (e.g. Study 190-026, a pivotal transient insomnia trial). This "Evaluable" population was defined in the study report for Study 190-026 as follows: *this population was identified by Availability Committee based on blinded review of protocol deviations prior to unblinding.* A number of efficacy trials (includes pivotal trials) selected subjects who were identified as "important" protocol deviators which consisted of the majority of subjects in some major efficacy trials (e.g. 66% of subjects in Study 190-046). Some protocol deviations in some studies included giving active ESZ drug to placebo subjects. It is not clear which subjects were selected for inclusion in the data analyses of primary and key secondary variables of the efficacy trails in this submission. This is an issue that needs to be addressed.
- Statistical methods, described in the study reports of several efficacy trials were not clear or a clear rationale for using the statistical methods selected for primary analyses in efficacy trials, generally could not be found (e.g. a clear statement as to whether the last-carried-forward observation was used for the primary analyses, whether mean or median values were used for the primary analyses, among other aspects of the statistical methods).

Given the above biometric-related issues this reviewer describes efficacy results and statistical methods as found in the corresponding sections of the study reports.

Refer to the reviews of each respective reviewer for details, conclusions and recommendations (their reviews are pending at this writing).

III. Human Pharmacokinetics and Pharmacodynamics

This submission is under review by the OCPB Reviewer. The following summarizes information, as provided by the sponsor.

A. Pharmacodynamics

The ESZ is a non-benzodiazepine pyrrolopyrazine derivative of cyclopyrolone, which is believed to primarily act as an indirect GABA agonist. ESZ binds to the macromolecular, GABA-benzodiazepine-receptor complex and is believed to act by indirectly potentiating GABA stimulated chloride conductance. Increased chloride conductance results in a hyperpolarization and in turn, inhibition of normal transmission. ESZ is reported to show greater affinity for alpha-1 and alpha-3 GABA subunits, with a weak affinity to alpha-2 and alpha-5 subunits. The alpha-3 GABA subunit is found in the brainstem based on preclinical results showing greater expression of this particular subunit in the brainstem. The regulation sleep, involves brainstem structures.

B. Human Pharmacokinetics

Pharmacokinetic (PK) studies of young healthy adults using single doses of up to 7.5 mg in multiple daily doses of 1, 3, and 6 mg administered over seven days revealed the following results as summarized by the sponsor:

- Tmax = approximately 1 hour.
- $T_{1/2}$ = approximately 6 hours.
- No accumulation with multiple daily dosing over seven days.
- Dose proportional kinetics at doses ranging from 1 to 6 mg.

ESZ is metabolized by:
- Oxidation.
- Demethylation.

In vitro studies show the following hepatic CYP enzymes involved with metabolism of ESZ:
- CYP 3A4
- CYP 2E1 .

The following summarizes results on excretion of either the racemic compound (zopiclone) or ESZ (as specified in the following):
- 75% of racemic (zopiclone) administered orally, is found in the urine, primarily as metabolites.
- 10% of ESZ, administered orally, appears in the urine as parent compound.

The following describes food effects after high-fat diet in PK parameters observed in trials on ESZ:
- No change in $T_{1/2}$
- No change in AUC
- Decreased Cmax by 21%.
- Increased Tmax by 1 hour.

According to the Biopharmaceutical Reviewer (OCPB) studies show evidence that interconversion between isomers does not occur with ESZ or with ZOP (per e-mail communication dated 8/4/03). Also, the OCPB reviewer considers a 3 mg ESZ dose equivalent to a 7 mg dose of ZOP on PK parameters.

5. Drug-Drug Interaction Results.
The metabolism of ESZ was previously described above. The following results are described in proposed labeling:
- No PK or PD interaction was observed with coadministration of ESZ and each of the following drugs: paroxetine, digitoxin, warfarin, and lorazepam.
- While, no interaction effects on PK were observed with ESZ and olanzapine an interaction effect on a pharmacodynamic measure of psychomotor function.
- A 2.2-fold increase in exposure to ESZ occurred during coadministration of ESZ and 400 mg ketoconazole (a potent CYP3A4 inhibitor).
- The clearance of drugs metabolized by common CYP 450 enzymes is not expected to be altered by coadministration with ESZ.

6. Special Populations.
Age Effects.

A 41% increase in AUC is observed in elderly subjects (over 65 years old) compared to young subjects. Elimination of the study drug was also prolonged to approximately nine hours, while Cmax showed no change. Given these results the sponsor recommends the dose of 2 mg in the elderly, as compared to a recommended dose of 3 mg in non-elderly adults.

Gender Effects.
No gender effects on PK of ESZ were observed.

Effects of Hepatic and Renal Impairment. Subjects with severe hepatic impairment demonstrated an increase in AUC by approximately 74% and in T1/2 to 14 hours, but no change in Cmax or Tmax, compared to healthy subjects. Based on these findings the sponsor recommends a 2 mg dose in patients with severe hepatic impairment.

A 29-47% increase in AUC and an 8-25% increase in Cmax were observed in subjects with renal impairment. However, because of a large overlap on PK values between these subjects and healthy subjects, the sponsor does not recommend a dose adjustment in patients with renal impairment.

Other Pharmacodynamic Properties of ESZ or ZOP
Sections VI-VIII of this review describe pharmacodynamic (efficacy and safety) results of clinical trials.

IV. Description of Clinical Data and Sources
A. Overall Data: Materials from NDA/IND

The following items were utilized during the course of this clinical review:

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
January 30, 2003	• NDA 21-476, an electronic submission and also a hard copy of volume 1 (cover letter, table of contents, References 1-16) and of volumes of the Study report for Study 190-016 (the abuse liability study under review by CSS). The electronic submission includes the following major sections: 2(labeling), 3 (summary), 4 (CMC), 5 (pharm/tox), 6 (hpbio), 8/10 (clinstat), 13 and 14 (Patent information and certification), 16 and 17 (Debarment and Field Copy certification), 18 (User Fee cover sheet), 19 (Financial information) and 20 (Other). Case Report Tabulations and Case Report Forms (CRFs) are in sections 11 and 12 of the submission. • Amendment submissions dated: 3/18/03, 3/19/03, 3/24/03, 3/25/03, 5/29/03, 6/13/03, 6/18/03, 6/30/03, 7/15/03, and 7/25/03. Some of these submissions were responses to questions from other reviewer's and were not reviewed by the Clinical Reviewer (refer to CMC and Pharmacology reviews). •The 6/30/03 submission was the 120-day Safety Update submission. Several amendment submissions were revised study reports with information about errors that were found in clinical and non-clinical sections in the original submission. •The 5/29/03 Amendment submission was regarding PSG data listings that were "inadvertently" not included in the study report of Study 190-046 of the original submission. The sponsor provides an amended study report for this study, containing "all data sets for PSG results". However, the review of the study reports submitted with the original NDA was already review by the time the amended study report was received. Since, the omissions in the amended version did not involve summary tables and text sections of the study report (as described in the cover letter of the 529/03 submission) this review reflects study results as described in the originally submitted study report for Study 190-046.

B. Tables Listing the Clinical Trials

Phase I trials are described in Section VIII on "Integrated Safety Information" involving 295 ESZ treated subjects and 124 Placebo treated subjects in the ITT Safety Population. 226 of the 295 ESZ treated subjects received at least a single dose of ESZ at a dose level of at least 3 mg (some subjects received dose levels as high as 7.5 mg). Table VIIIA1 in the appendix, enumerates subjects in the Safety Population in each trial (as provided by the sponsor).

Phase III Efficacy or Safety Trials. The following Tables IV.B.1.a-c shows the breakdown of the ITT Safety Population by dose-groups or dose-levels for Studies of Non-Elderly Healthy Adults (Table IV.B.1a), Chronic Insomnia Trials of Non-elderly Adults (Table IV.B.1b), and Chronic Insomnia Trials in Elderly Adults (Table IV.B.1c).

Tables IV.B.1a Clinical Studies in Healthy Non-Elderly Adults†

Protocol/ Study Population (popn)	Study Design	Treatment (Tx) Groups (Grps) or Conditions (oral tablet unless otherwise specified)	N(Completers)/Tx Grp or Condition (% of ITT Safety Popn)	N (ITT Efficacy Popn)*/Tx grp or Condition	N (ITT Safety Popn)**/Tx grp or Condition
Studies on Next-Day Effect Studies (Cross-over and Parallel Group)					
190-024 **Inpatient Study on Next-Day Performance Effects in Healthy Non-Elderly Adults**	SC, DB, SD, 4-Way X-over, Random., Plac Ctled in Males and Females	2 or 3 mg ESZ 30 mg Flurazepam Placebo	12		12
190-025 **Inpatient Study on Next-Day Performance Effects** **Non-Elderly Adults with Chronic Insomnia**	Single Center, SD, 4-Way X-over, DB, Random., Plac Ctled in males and females	2 or 3 mg ESZ 30 mg Flurazepam Placebo	**Total: 12**	12 12 13	**12-13**
Transient Insomnia PSG Studies (Parallel Group)					
190-026 **Efficacy and Safety, First Night Effect Study** **Healthy non-Elderly Adults (25-50 yo)**	MC (15 sites), SD, DB, Parallel Grp, Random., Plac Ctled	SD 1 mg ESZ solution 2 mg ESZ solution 3 mg ESZ solution 3.5 mg ESZ solution Placebo	47 (100%) 97 (100%) 98 (100%) 96 (100%) 97 (99%) **Total: 337**	47 97 97 96 98 **Total: 337**	47 97 98 96 98 **Total: 338**

† Abbreviations: Ctled=controlled, DB = Double-bind, Grp=group, MD = multiple-dose, MC=multicenter, OL=Open-label, Plac=placebo, Popn = population, PSG=polysomnography, rand.= randomized, SD=single-dose, Tx=treatment, x-over=crossover, yo=years old

*ITT Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline Montgomery Asberg Depression Rating Scale assessment.

**ITT Safety Population: randomized subjects having at least one dose of double blind study drug.

Table IVB1b. Chronic Insomnia Trials in Non-Elderly Adults†					
PSG Cross-Over Trials in Non-Elderly Adult Patients with Chronic (Primary) Insomnia					
Protocol/ Study Population (popn)	**Study Design**	**Treatment (Tx) Groups (Grps) or Conditions (oral tablet unless otherwise specified)**	**N(Completers)/Tx Grp or Condition (% of ITT Safety Popn)**	**N (ITT Efficacy Popn)*/Tx grp or Condition**	**N (ITT Safety Popn)**/Tx grp or Condition**
190-045 **Efficacy PSG Study** **Non-Elderly Adults with Chronic Insomnia**	MC (7 sites), DB , 2-Day dosing per Treatment Condition/Visit, 6-Way X-over, Random., Plac Ctled	2-Day Tx Conditions: 1 mg ESZ 2 mg ESZ 2.5 mg ESZ 3 mg ESZ Placebo group	**Total: 63 (97%)**	**63-64/Condition**	**Total: 63-65/condition**
6-Week (44 nights) PSG Parallel Group Trial in Non-Elderly Adult Patients with Chronic (Primary) Insomnia					
190-046 **Efficacy and Safety, PSG/Outpatient Study** **Non-Elderly Adults with Chronic Insomnia**	MC (51 sites), MD (44 Days), DB, Parallel Grp, Random., Plac Ctled	44 Days Treatment-Last PSG visit on Treatment Day 29: 2 mg ESZ 3 mg ESZ Placebo group	 97 (93%) 101 (96%) 94 (95%) **Total: 292**	 104 105 99 **Total: 308**	 104 105 99 **Total: 308**
Long Term (6 months DB, 6 months Open Label Extension) Sleep Diary, Outpatient, Parallel Group Trial in Non-Elderly Adult Patients with Chronic (Primary) Insomnia					
190-049 **A Safety & Efficacy Sleep Diary/Outpatient Study** **Non-Elderly Adults with Chronic Insomnia**	MC (69 sites), Random., Plac Ctled, MD, 6-month DB-Parallel Grp Phase, then 6-month Open Label Extension non-Plac Ctled, Phase	6-months DB Phase: 3 mg ESZ Placebo group 6-months Open Label Extension Phase (OL): 3 mg ESZ	6-months DB Phase: 360 (61%) 111 (57%) **Total: 471** 6-months OL ESZ: 382 (81%) DB & OL ESZ: 12 mo. ESZ: 296 6 mo. Placebo & 6 mo. ESZ: 86	6-month DB Phase: 593 195 **Total: 788** 6-months OL ESZ: 471 DB & OL ESZ: 12 mo. ESZ: 360 6 mo. Placebo & 6 mo. ESZ: 111	6-month DB Phase: 593 195 **Total: 788** 6-months OL ESZ: 471 DB & OL ESZ: 12 mo. ESZ: 360 6 mo. Placebo & 6 mo. ESZ: 111

† Abbreviations: Ctled=controlled, DB = Double-bind, Grp=group, MD = multiple-dose, MC=multicenter, OL=Open-label, Plac=placebo, Popn = population, PSG=polysomnography, rand.= randomized, SD=single-dose, Tx=treatment, x-over=crossover, yo=years old

*ITT Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline Montgomery Asberg Depression Rating Scale assessment.

**ITT Safety Population: randomized subjects having at least one dose of double blind study drug.

Table IV.B.1c. Chronic Insomnia Trials in Elderly Adults†					
2-Week Sleep Diary or PSG Parallel Group Studies in Elderly Outpatients with Chronic (Primary) Insomnia					
Protocol No and Study Population	**Study Design**	**Treatment (Tx Groups or Conditions (Oral)**	**N (Completers) per Tx group or Condition (% of ITT Efficacy Pop.*)**	**N (ITT Efficacy Pop.) * per Tx group or Condition**	**N (ITT Safety Pop.) ** per Tx group or Condition**
190-047 **2-Week PSG Efficacy and Safety Study** **Elderly Adults (65-86 yo) with Chronic Insomnia**	MC (48 US sites, 2 Canada sites), DB,2-week MD, Parallel Group, Random, Plac Ctled	1.5 mg ESZ (aborted) 2 mg ESZ Placebo group	Aborted @ n=28 133 (98%) 122 (95%) **Total: 283**	 136 128 **Total:264**	28 136 128 **Total: 292**
190-048 **2-Week Sleep Diary Efficacy and Safety Study** **Elderly Adults (64-85 yo) with Chronic Insomnia**	MC (32 sites), DB, 6-week MD, Parallel Group, Random, Plac Ctled	1.0 mg ESZ 2 mg ESZ Placebo	67 (91%) 70 (89%) 73 (90%) **Total: 210**	72 79 80 **Total: 231**	72 79 80 **Total: 231**

† Abbreviations: Ctled=controlled, DB = Double-bind, Grp=group, MD = multiple-dose, MC=multicenter, OL=Open-label, Plac=placebo, Popn = population, PSG=polysomnography, rand.= randomized, SD=single-dose, Tx=treatment, x-over=crossover, yo=years old

*ITT Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline Montgomery Asberg Depression Rating Scale assessment.

**ITT Safety Population: randomized subjects having at least one dose of double blind study drug

Studies 190-012 and 190-016 are not shown in the above in-text tables. These studies were small trials focusing on specific safety issues (respiratory drive effects or alcohol-ESZ interaction effects on psychometric test performance) and are described later in this review.

C. Post-Marketing Experience

The sponsor has the following active applications for the development of ESZ submitted to foreign countries (INDs): — The sponsor also has the US INDs that are currently active (INDs 58,647 — There are no other active investigational or marketing applications described in the submission. The submission also does not describe any past foreign applications on ESZ, although this is not explicitly stated (only reference is made to "active" submissions).

Zoplicone (ZOP) is a cyclopyrrolone approved in 85 foreign countries for the market (since 1987). Also refer to section IA for approved dose/formulation and indication. In the cover letter of the submission the sponsor states that ZOP has "never been withdrawn from the market for reasons related to safety." Approval of ZOP in a foreign country is not pending (as of 1/2002), and approval of an application in a foreign country (referred to by the sponsor as a "registration dossier") has never been refused (as described in Section 3.C of the summary.pdf of the submission).

/

D. Literature Review

The sponsor was informed during the prefiling stage of this NDA that a complete review of the literature (with a description of methods employed and the results of a review of the literature) could not be found in the submission. The sponsor responded to this deficiency in a 3/24/03 amendment submission in which they state that they have conducted a "comprehensive review of worldwide literature on racemic zopiclone." The sponsor indicates that any potential safety signals revealed from the literature review are "commented upon in section 8 ./10 .B .1.4 of the original submission. Section 8./10 of the submission is entitled, clinical Data/Statistical Section and the subsection 8./10.B.1.4 is entitled "Potential Efficacy and Safety Issues of Sedative/Hypnotics" on pages 87-88 in the clinsum.pdf file. Instead, the section focuses on a description of the symptoms of insomnia, and on the efficacy trials that were conducted on ESZ to support the proposed indication. A listing of study reports is provided. This section also lists sections of the submission related to specific aspects of safety, primarily citing study reports or the ISS which describe results of clinical trials (not a review of the literature).

Subsection 8./10.B.1.4 also provides a listing of topics citing other sections of the submission on the following topics, but a review of the literature is not listed: drug abuse and overdose information, pregnancy and lactation, and psychiatric populations were among topics that were listed. This subsection also cited study reports and other subsections, but does not describe a review of the literature or reference a section on this topic.

Attachment II of the 3/24/03 amendment submission, provides some discussion of selected articles in the literature on the racemic zopiclone. However, a review of the literature on ESZ and a discussion of what exists in the literature on this enantiomer cannot be found in this amendment submission (after filing of the NDA) or in the original NDA submission. During teleconference communications with the sponsor (during the prefiling phase of the NDA), the sponsor clarified that no publications on ESZ could be found.

Section VIII.P of this review describes the information provided by the sponsor in the 3/24/03 amendment submission and in section 8 ./10. B .1.4 section of the original submission.

V. Clinical Review Methods

A. Materials Reviewed.

Refer to Section IV, above, regarding materials utilized for this review and for a summary of the clinical trials described in the submission.

B. Adequacy of Clinical Experience.

The sponsor's trials meet ICH guidelines for overall, 6-month and 1-year exposure for the 3 mg dose (— , based on an enumeration of subjects in the sponsor's clinical trials, as described in more detail in Section VIIIC of this review (also provides additional information on drug exposure in the trials). The NDA includes a number of efficacy trials on non-elderly and elderly patients with Chronic Insomnia, a transient insomnia trial, a number of Phase I trials, and trials focusing on specific safety issues as described in the previous Section IVB. The ITT Efficacy and Safety Populations were of adequate size (as previously shown in summary tables in Section IVB). Therefore, the sponsor's experience with ESZ at the recommended dose level of 3 mg for short term treatment in patients with Chronic Insomnia appears to be adequate.

C. Data Quality and Completeness

A number of problems were found with this NDA submission impacting on the quality and the completeness of the submission that in the opinion of this reviewer was not adequate (refer to Section XI for conclusions and recommendations) regarding this issue. The following outlines some of these problems (additional problems are also provided in other sections of this review):

1. Errors in Study Reports. A number of Clinical Study Reports (CSRs) had a number of errors in which these CSRs had one or several Errata documents (provided as separate documents) in the original submission listing uncorrected errors that existed within each given CSR. In response to this issue, the sponsor provided CSRs for several studies in a 3/25/03 amendment submission incorporating corrections to the errors listed in errata documents. Other errors were found in the CSRs, but were generally clarified or corrected. However, other problems regarding the data and concern about the accuracy of the information that were found in the submission, as described in various sections of this review with some of the problems described below.

Subsequent to the above, the sponsor submitted an amendment under the NDA, later in the review cycle (dated 5/29/03) with polysomnography data listings of subjects that were "inadvertently" not included in tabular listings in the 190-046 Efficacy Study CSR.

Also see some other examples below.

2. Problems with the ISS. The ISS of the submission had several problems with regards to the quality and completeness of this part of the NDA. The following are examples:

- For example, the incidence of subjects who had abnormal values on clinical assessments in each treatment group could not be found for most trials in the ISS. For most studies

(or integrated trials), shift tables were provided, but this information or information on outliers could not be found for all parameters.

- Descriptive statistical results generally included a post randomization time point after double-blind treatment was discontinued (several days to approximately one week post-dose). The sponsor provided some selected descriptive statistical results that included on-treatment data in the 120-Day Safety Update submission dated at 6/30/03.
- Information (with data and results) on potential drug effects on orthostatic vital sign measures could generally not be found.
- One area of concern to the Division, as expressed to the sponsor during pre-NDA meetings, is potential endocrine effects of the study drug, such as effects on reproductive hormones (as observed in some preclinical studies). Yet when a spot check on the incidence of gender specific AEs was conducted by this reviewer for Study 190-049 the incidence provided in several tables had values consistent with using the entire sample size of subjects in the denominator (rather than using the appropriate gender for sample size in the denominator for determining the incidence of the given AE). These observations are described in greater detail in Section VIII of this review.
- Other problems with the ISS are described in the safety section of this review (Section VIII). Some safety data that is generally found in the ISS was scattered and found in other places (such as the study report) or in amendment submissions or could not be found (refer to Section VIII).
- Refer to Section VIII for additional problems and a more detailed description of problems with the ISS.

3. A review of the literature could not be found in the submission as follows. A complete review of the literature on ESZ and ZOP cannot be found in the original submission. In response (in a 3/24/03 amendment submission) to inquiries regarding a review of the literature, the sponsor specifies subsection 8 ./10 .B.1.4 as the location where a review of the literature could be found in the original submission. While this subsection listed topics with citations (e.g. study reports and other errors sections of the submission), this listing did not include a review of literature for either the racemic or enantiomer of the study drug. It appears that any mention of the literature in the submission is scattered throughout various sections in the submission, such that the information is fragmented. A description of the results of a review of the literature on the enantiomer cannot be found. The following is described in Section VIIIP of this review regarding information the sponsor provided in response to our inquiry regarding a review of the literature for both ESZ and zopiclone:

This section describes the contents of Attachment II of the 3/24/03 amendment submission responding to inquiries about a review of the literature on ESZ and zopiclone, since a section on a review of the literature could not be found in the original submission. Section 8 ./10. B.1.4., is cited (in the 3/24/03 amendment submission) as the location where a review of the literature can be found in the original submission. This subsection of the review summarizes the information that was found in Section 8 .\10 .B. 1 .4. In summary the information found in this subsection appear to be a mixture of information obtained from different sources (results of the sponsor's clinical trials, results of trials on zopiclone, pharmacovigilance data or postmarketing data on zopiclone, and perhaps information from the literature, although this is not clear, as described below). Since it is not clear to him to this reviewer at what information was specifically information from a review of the literature in Section 8 .\10 .B.1 .4, the information found in this

section and in subsections cited in Section 8.\10 .B. 1.4 are described below, independent of the source from which it was obtained.

Furthermore, methods of a search on either the racemate or the enantiomer with a listing of publications as a result of this search could not be found. Although, the 3/24/03 amendment submission provided some summary information on particular topics based on a review of the literature on ZOP (but was not complete). The sponsor indicated verbally during a pre-filing meeting that no articles on ESZ could be found in the literature (although a statement regarding a literature search on ESZ and methods employed for the literature search could not be found in the submission).

4. Enumeration of events of neoplasia and classifying the events as adverse events or adverse dropouts, with none of these events classified, as serious adverse events. Refer to Section VIII and XI for details on problems with the information or the manner of the information provided on this topic. Aside from problems in enumerating these events, it is not clear why events of neoplasia were not classified as SAEs (only classified as adverse dropouts or adverse events), as described in more detail in Sections VIII and XI of this review.

It is also notable that the one longterm trial conducted by the sponsor (Study 190-049) employed stringent eligibility criteria and screening methods for patients at risk of neoplasia that is not generally used for trials intended to examine longterm safety. A rationale for the use of these unusual methods could not be found and these eligibility criteria were not listed under the section on inclusion and exclusion criteria in the study report, but rather, were found in a section on methods for each study visit, as described in more detail later in this review (Sections VI and VIII).

5. Multiple problems with efficacy data, the study design relevant to the quality of the study and the data. Some of these problems are the following but refer to other sections of this review for more problems (such as those described in Section XI and Attachment I of this review and other sections):

- Some subjects given a stock solution of "zopiclone" of an unspecified dose when subjects in the study were to receive placebo or ESZ, per protocol.
- Some subjects were selected in some studies as "evaluable" while others were identified as "important protocol" deviators, despite the protocol already having pre-specified criteria for protocol violators. Some data from some of these subgroups was used for some of the primary efficacy analyses and other data was used for secondary or "key" secondary analyses (see sections below and Section XI for details).
- Despite results on unpleasant taste for an drug-related and dose-dependent effect (on incidence of this event), a discussion of these results relative to the impact such an effect can have on the double-blind study design could not be found in the submission. See Section XI for details.

6. Investigator listings do not match. The following comparisons were made with the results of these comparisons described:

- The investigator listings for Studies 190-045 and 190-049 compared to the list provided in the financial information section of the submission (Table 19.1-1 on page 4 of the

other\financial.pdf file) revealed the following three investigators is being listed in the financial disclosure table, but not in the study site/investigator summary tables:

- Scott Bonvallet, M.D. of Study 190-049 .
- Martin Scharf, Ph.D. and James Walsh, Ph.D. of Study 190-045.

Perhaps the above investigator/sites did not have any randomized subjects and were therefore not listed as an investigator site for their corresponding studies. Further clarification on this isn't consistency should be obtained, as described in the final section of this review (Section XI).

7. Postmarketing data was provided as periodic safety update reports. A summary of the incidence of safety alerts by AE terms and did not provide a description of any unexpected findings or did not conduct specific searches for events that may be of concern (e.g. potential hormonal effects and reports of neoplasia, given the observations in preclinical trials).

8. See Section XI and other sections of this review, as well as Attachment 1 for other areas relevant to data quality and/or completeness. Also, at the time of this writing the sponsor a response to all items in the 74-Day Letter cannot be found including the amendment submission that was subsequently submitted with reference to this 74-Day letter (the 120-Day Update Report submission).

9. Information that is typical of an NDA or is required could not be found in the original submission or was presented in the fragmented manner that was difficult to decipher. See above for some examples and examples can be found in other sections of this review.

D. Evaluation of Financial Disclosure

In summary, the sponsor does not provide any significant financial disclosure information that would be considered as significantly impacting on the interpretation of safety and efficacy findings in their trials, as described in the following.

The sponsor reports that none of the investigators of their trials received financial compensation under any of the four categories (Categories 1-4) on the Financial Disclosure Form, Form FDA 3454 (note that Categories 2 and 4 specify a cut-off amount exceeding $25,000 and $50,000, respectively, for a given investigator to be considered as receiving a significant payment or equity interest, respectively). This statement pertains to all principal investigators and subinvestigators (as well as, to any spouses or dependent children of these investigators) of all completed and ongoing ESZ studies. A summary table listing the principal investigators that completed to the financial disclosure form is provided in the financial disclosure section of the submission. The sponsor only lists three study sites (listed by principal investigator) from which they attempted to contact for update information and received no response (updated information was requested since the original financial disclosure forms were completed before the cutoff date for the NDA). All three sites were study sites for the only transient insomnia trial, Study 190-026, for this NDA intended to support the proposed transient insomnia claim. These sites completed the forms upon the sponsor's initial request, and at that time, indicated they had no disclosable financial interest (they did not check any of the four categories).

A few inconsistencies between investigator listings (based on a spot check comparison for Studies 190-049 and 190-045 as described in the previous section of this review on data quality and completeness (subsection C). However, the information as provided by the sponsor does not reveal any remarkable findings that would significantly impact on the safety or efficacy

results of the sponsor's trials in this submission. Although, clarification on these inconsistencies should be sought (as discussed in the final section of this review, Section XI).

VI. Integrated Review of Efficacy

A. Review of Studies for Which Efficacy Claims Are Made

Section IVB outlines Phase III efficacy trials that were used by the sponsor to support proposed insomnia claims. A transient insomnia claim is proposed based on polysomnography (PSG) efficacy data from Study 190-026. This trial was a multicenter, single-dose, placebo controlled, parallel group, double-blind, randomized trial conducted. The study employed a first night effect, transient insomnia model to examine effects of a single-dose of ESZ (1, 2, 3, and 3.5 mg of ESZ oral solution) compared to placebo treatment on primary and secondary PSG measures.

Several short-term and longer term trials were conducted to support insomnia efficacy claims of ESZ (a tablet formulation) in patients with Chronic Insomnia. These multi-center trials employed a randomized, placebo-controlled, double-blind study design using PSG objective efficacy measures and/or subjective efficacy measures from sleep questionnaires. These studies are summarized in the following paragraphs. Some trials examined next-day effects or rebound effects of the study drug compared to placebo.

Study 190-045 was a PSG trial that involved six treatment conditions using a 6-way crossover in which subjects received two consecutive nightly doses of each of the following doses: placebo, 1, 2, 2.5, and 3 mg of ESZ. Study 190-046 was a 6-week, parallel group trial with the following three treatment groups (assigned study drug taken at bedtime): placebo, 2 mg and 3 mg ESZ. While sleep diary efficacy measures were obtained over the 6-week double-blind phase of the trial, PSG efficacy measures were obtained at multiple time-points with the last time-point at Day 29 of treatment. Therefore, the primary analyses from which proposed efficacy claims only reflected data collected at 4 weeks and not at 6-weeks of treatment, as the primary analyses was conducted on PSG data and not on subjective sleep diary data (which was collected over the 6-week treatment phase).

Other Phase III trials were two 2-week trials that were conducted to support proposed efficacy claims for the treatment of Chronic Insomnia in elderly patients (Studies 190-047 and -048). Study 190-047 employed PSG efficacy variables, while Study 190-048 employed sleep diary measures.

A long-term trial was employed in non-elderly patients with Chronic Insomnia that had a 6-month double-blind phase followed by a 6-month open-label ESZ phase. This trial employed sleep diary efficacy measures and was primarily intended to establish long-term safety.

B. A Description of Investigators/Sites, Subject Disposition, And Overall Demographic Features in "Pivotal" and "Supportive" Efficacy Trials.

1. Investigators and Sites of Efficacy Trials

See Tables VI.B.1-VIB3 in the appendix (as provided by the sponsor) for the listing of study sites and the investigators for selected efficacy trials 190-026, 190-045 and 190-049[2] (as provided by the sponsor). Investigator listings for other efficacy trials were provided in the submission.

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[2] Because of the number of efficacy trials, investigator listings of only 3 trials are shown in the appendix of this review.

2. Subject Disposition in Efficacy Trials

Refer to Tables VI.B.4-VIB9 in the appendix for the enumeration of subjects by disposition categories for each efficacy trial. Treatment groups were generally similar on the incidence of subjects within each disposition category among the studies with some exceptions as discussed in the following (and as shown in the summary tables in the appendix). As shown in the summary tables it generally appears that any treatment group difference observed in the overall incidence of dropouts in a given study was primarily reflecting group differences in either or both of the following disposition categories:

- Incidence of AE's (generally occurring more often in the ESZ groups with an incidence of up to 13% compared to placebo which had an incidence of up to 6%) and/or
- The incidence of voluntarily withdrawals (e.g. 26% of ESZ subjects compared to 14% go to placebo subjects in Study 190-049).

It is not clear what the "voluntary withdrawal" category represents. Perhaps, this category includes subjects that withdrew due to lack of efficacy, as this disposition category was not found in most of the disposition tables (except for Table VI.B.6 of Study 190-046, as shown in the appendix). Several subjects in some of the trials (generally 1% or less in a given treatment group) fell under the category of "other." It is not clear what this category represents (an explanation for this category could not be found in).

Finally, one critical observation is that two subjects in Study 190-047, each participated in the study at two different sites under different subject identification numbers for each of the two sites as follows (presumably these subjects underwent the study on two separate occasions rather than participating at two sites, simultaneously):

- Subject 172710 at study site 172 received 1.5 mg ESZ and also received 2.0 mg at study site 186 under the subject number of 186704.
- Subject 169705 received 2.0 mg of ESZ at site 169 and also received a placebo at site 174 under the subject number of 174729.

The sponsor does not specify that the data from the subjects were deleted from the efficacy data-set.

Further clarification is needed from the sponsor regarding the disposition categories of "other" and "voluntary withdrawal." Also clarification on how efficacy data was handled from these subjects is needed. A discussion of determining "evaluable" subjects was found in the study report of some studies as previously described in Section IVC and in sections that follow.

3. Overall Demographic Features of Subjects in Efficacy Trials.

Refer to Tables VIB10-VIB16 in the appendix for a summary of demographic features (age, gender, race, height, weight, and BMI) of subjects in each treatment group of each efficacy trial (as provided by the sponsor).

<u>Demographic Features In Non-Elderly Chronic Insomnia Trials (190-045, 190-046, 190-049).</u> As shown in the summary tables in the appendix, the majority of subjects in the three trials of non-elderly patients with Chronic Insomnia were female. The mean age of subjects was approximately 40 years old. Demographic features were generally similar across treatment groups and across efficacy trials involving non-elderly patients with Chronic Insomnia with some exceptions noted in the following. Some of the efficacy trials varied in the following categories:

- In the distribution of subjects across ethnic categories (the majority of subjects were Caucasian, while the studies differed primarily in the incidence of subjects within the "Hispanic" and "Black" categories).
- In the mean and median age of subjects in nonelderly adult Chronic Insomnia trials (subjects in the long-term trial Study 190-049 had a mean age and median ages of 44 and 45 years old, respectively, with a range of 21 to 69 years old, compared to subjects in other adult patient trials, 190-045 and 190-046 in which the mean and median age of the subjects was approximately 39 and 40 years old, respectively).
- Small differences across trials in the distribution of subjects by gender.
- As shown in the summary tables some studies showed significant treatment group differences in some of the demographic features (BMI, incidence of male and female in subjects, and weight). However, most of these differences were small in magnitude.

Demographic Features In Elderly Chronic Insomnia Trials (Studies 190-047 and 190-048). Tables VIB14-VIB15 summarizes demographic features in the two efficacy trials in elderly patients with Chronic Insomnia. These trials generally appear to show similar results on demographic features across the trials and across treatment groups within each trial. Subjects were approximately the mean age of 72 years old (median age of approximately 71 or 72 years) and were primarily Caucasian (generally over 90%) and female (approximately 60%).

Demographic Features in the Transient Insomnia Trial (190-026). As shown in Table VI. B.16. in the appendix (as provided by the sponsor), subjects in the Transient Insomnia trial (a study on healthy adults) had a mean age of approximately 34 years old (age range of 20-54 years), with the majority is subjects being Caucasian and female.

C. Non-Elderly Chronic Insomnia Trials (Studies 190-045, 190-046 and 190-049)
Objectives, Study Design and Efficacy Results. Studies 190-045, 190-046 in 190-049 are multicenter trials conducted on nonelderly adults (21-64 years old) with Chronic Insomnia (by DSM-IV criteria). The primary objective of these trials was to demonstrate efficacy on latency to persistent sleep (LPS), as assessed by polysomnography (PSG; in Studies 190-046 and 190-045) or by subjective LPS, as assessed by sleep diaries (in Study 190-045). All three trials used a fixed-dose design with nightly bedtime doses of ESZ ranging from 1 mg (in Study 190-045) to a dose of up to 3 mg.

One key difference between these non-elderly Chronic Insomnia trials was in the duration of the double-blind treatment phase. The double-blind phase of the PSG parallel group Study 190-046 was for 44 nights compared to only two nights (for each treatment condition) employed in the cross-over trial, Study 190-045. However, the last PSG recording conducted in Study 190-046 was on Day 29, such that primary efficacy results only reflect observations out to 4-weeks, rather than 6-weeks of double-blind treatment.

Study 190-049 was a long-term study of six months of double-blind treatment followed by a six month open label phase. Another primary difference between these trials is that the sponsor employed a parallel group design in Studies 190-046 and 190-049, while employing a 6-way cross-over design in Study 190-045.

All of the trials examined next-day effects using morning questionnaires. The 6-week trial (Study 190-046) also examined next-day effects on the Digit Symbol Substitution Test

(DSST) and rebound effects over two consecutive nights of single-blind treatment following the double-blind treatment phase.

These trials and study results on efficacy, next-day effects, tolerance, and rebound effects (as examined in Study 190-46) are described in more detail in the following subsections. Withdrawal AEs was found in the study report of Study 190-046 and 190-047 and these results are also summarized below. Withdrawal AEs for Study 190-049, the longer term trial, which did not have a single-blind withdrawal phase (the study had a follow-up phase) were provided in a 120-Day Safety Update report (amendment submission dated 6/30/03). These results are described in the Integrated Safety section of the review (Section VIII). Refer to Section VIII for other safety results from these efficacy trials.

1. Study 190-045

This study is described based on an amendment submission that provided a corrected version the study report for this study, since the original submission had attached listings of errors within the study report (referred by the sponsor as "Errata" attachments).

Study 190-045: Objectives

The primary objective of this study was to show efficacy on LPS as determined by PSG measures in adults with Chronic Insomnia.

Study 190-045: Study Design and Subjects

This was a multicenter (7 study sites), double-blind, placebo-controlled, randomized, active comparator (10 mg zolpidem), PSG study employed a Williams crossover design (a balanced residual effects design in which every order to pair of treatments occurred an equal number of times over successive treatment periods). The study was conducted on 21 to 64-year-old, generally healthy, patients who met to DSM-IV criteria for Chronic Insomnia and other eligibility and PSG criteria (after undergoing a 3-night PSG screening phase). The study involved the following phases:

- A 3-night, single-blind placebo, PSG screening phase.
- Six double-blind treatment conditions with each condition involving 2 nights of PSG and nightly doses of assigned study drug for the given treatment condition (a 3-7-day washout period occurred between each treatment condition).

Subjects who met PSG eligibility criteria after the three night screening phase, returned to the study site three to seven days later to be randomized to a double-blind treatment sequence (of 6 treatment conditions) and to begin their first treatment condition. Each subject received each of the following treatment conditions (they received their nightly dose with 240 ml of water, given as two tablets, at bedtime which occurred 30 minutes prior to the start of the PSG recording):

- Placebo
- 1 mg ESZ
- 2 mg ESZ
- 2.5 mg ESZ
- 3 mg ESZ.
- 10 mg Zolpidem

ESZ was administered as 1 mg or 1.5 mg tablets of the clinical service tablet formulation containing a number of excipients, as specified in the submission. The matching placebo contained all excipients.

Zolpidem was given as 10 mg tablets, but did not appear to contain the same excipients as the ESZ and placebo tablets (although this was not clearly described in the submission). The "observer" dispensing the study drug was partially blinded to the zolpidem. Individuals dispensing the study drug were not associated with other aspects of this study (i.e. did not conduct evaluations or were not responsible for the subject's care).

Subjects were randomly assigned (in a 1:1:1:1:1:1 ratio) to one of six treatment sequences ACBEFD, BDCFAE, CEDABF, DFEBCA, EAFCDB, and FBADEC (where A = placebo, B = 1.0 mg ESZ, C = 2.0 mg ESZ, D = 2.5 mg ESZ, E = 3.0 mg ESZ, and F = 10 mg zolpidem).

Eligibility criteria included the following requirements regarding the subject's sleep pattern over a period of at least one month prior to study entry:

- ≤6.5 hours of sleep/night
- > 30 minutes to follow sleep each night

Subjects also had to meet the following criteria over the 3-night PSG screening phase:

- An LPS of ⩾ 20 minutes over at least two nights that was not < 15 minutes on any of the three nights.
- Either a total sleep time of ≤ 420 minutes on at least 2 nights **or** a WASO of ⩾ 20 minutes on at least two nights that was not < 15 minutes on any of the three nights.

Additional criteria are described in the submission that include criteria for excluding patients with other sleep related conditions or specified psychiatric conditions (non-psychotic Axis I disorders were considered an individual basis, except for dementia and delirium), in addition to other criteria. The submission also includes exclusionary criteria regarding concomitant medications or other types of therapies. Subjects taking psychotropic agents or other medications known to affect sleep within three days prior to screening were excluded from the study.

Safety and efficacy assessments were conducted during this study according to the schedule shown in Table VIC1 in the appendix (as provided by the sponsor). On the PSG nights lights were turned off at 30 minutes prior to be getting the PSG recordings at a time-point that also corresponded to the median bedtime for the given subject (as determined from a daily sleep log completed by the subject over seven to 10 consecutive days prior the first PSG screening night on Visit 1). PSG recordings were conducted over an eight hour period after lights-off, upon which subjects that were still asleep at the end of the recording were awakened.

"Post-dosing" safety assessments (vital signs, AE recordings, and others) as shown in Table VIC1, were conducted on the morning after receiving the bedtime dose of study drug (at a timepoint that ranged from 9.0 to 10 hours after the previous night of dosing, and corresponded to 8.5 to 9.5 hours after lights-out, which was also 30 minutes-1 ½ hours after awakening in the morning). A standardized breakfast was given at 9 to 9.5 hours after dosing on the previous night (within 30 minutes after awakening). The Romberg test and heel-to-toe gait test were conducted after breakfast at 9.0 to 9.5 hours after lights-out. Orthostatic vital sign measures are not described among vital sign assessments conducted in this study.

"Next-Day Effects" Measures. The following "Next-Day Effects" were also obtained from data collected using the Morning or Evening Questionnaire (100 mm analog scales), or as otherwise specified (as shown in Table VIC2):

- Morning sleepiness in mm units (0 mm = "very sleepy" and 100 mm = "not at all sleepy").
- Daytime alertness in mm units (0 mm = "very sleepy" and 100 mm = "wide awake in alert").
- Daily ability to function in millimeters units (0 mm = "poor" and 100 mm = "excellent").
- Profile of Moods States questionnaire (POMS) that was modified in a manner of inquiring the subject about a time period of interest, rather then asking the subject about the previous week (as described in greater detail in the submission). Another modification of this scale for the purposes of the sponsor's trials was that scoring was based on the 1-5 scale, rather than and using the 0-4 scale of the original version of the POMS. Factor scores were obtained for each mood-state category (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment). These factor scores, excluding the vigor-activity factor score, were summated. A Total Mood Disturbance Score was obtained by subtracting the vigor-activity score from the summated factor score.

Study 190-045: Efficacy Assessments

Efficacy parameters included objective PSG, as well as subjective measures obtained from the Morning Questionnaire. These measures are described in more detail in Tables VIC3-VIC4 (in the appendix, as provided by the sponsor).

Sleep architecture was also examined in the trial.

Primary Efficacy Variable:

- LPS (PSG)

"Key Secondary" Efficacy Variable:

- Sleep Efficiency (PSG)
- WASO (PSG)

Study 190-045: Statistical Analysis of Primary and "Key Secondary" Variables

Data from the ITT population (randomized subjects who received at least one dose of study drug) was used for the primary statistical analyses. Data was ranked transformed for the primary analysis. Primary analysis was conducted to compare the three highest ESZ dose levels to placebo on the efficacy variable using an ANOVA model with treatment, sequences and visit as fixed effects. Subject nested within sequence was used as a random effect in this model. To determine an overall treatment effect this analysis was conducted for the three highest dose levels pooled (2.0 mg, 2.5 mg and 3.0 mg, using weights of - 3, 0, 1, 1, 1, 0, respectively) compared to placebo. Pair-wise comparisons were also conducted using the same ANOVA model to compare each of the four ESZ treatment conditions, and the zolpidem condition to placebo on the efficacy variable. To adjust for multiple comparisons, a Fisher's protected approach was used in which planned pairwise comparisons of each ESZ treatment condition to placebo were conducted after showing an overall treatment effect in the primary analysis at the level of significance of $p < 0.05$ (two-sided).

Secondary analyses were generally conducted using the same ANOVA model except that there was not an analysis for an overall treatment group effect before conducting pairwise comparisons, as described in the submission.

Study 190-045: Efficacy Results
Table VIC5 and Figure VIC1 in the appendix, summarizes the primary efficacy results showing highly significantly greater treatment effects on LPS in which the median LPS value was significantly less in each of the ESZ dose levels compared to placebo. Increasing dose levels of ESZ showed numerically decreasing median LPS values suggesting a dose dependent effect. The zolpidem condition was associated with the numerically smallest mean LPS value and median LPS value and a median LPS value that was smaller than all other treatment conditions, except for the high dose level of ESZ.

Additional efficacy measures including the objective WASO and sleep efficiency parameters, as well as other objective and subjective sleep parameters showed results that were generally similar to those revealed by the primary efficacy variable. The objective measure of Wake-Time-After-Sleep failed to show any significant treatment group effects for each of the ESZ dose levels or the zolpidem treatment condition compared to placebo. These results are summarized in Tables VIC5-VIC7 and Figures VIC1-VIC2 in the appendix (as provided by the sponsor).

Study 190-045: Results on the Incidence of Unpleasant Taste.
The following results are described since they may impact on the adequacy of the double-blind study design. The incidence of unpleasant taste in each treatment condition was as follows:

- 3 mg ESZ: 8%
- 2.5 mg ESZ: 9%
- 2 mg ESZ: 5%
- 1 mg ESZ: 5%
- Placebo: 2%
- 10 mg Zolpidem: 0%

Study 190-045: "Next-Day Effects"
The "next-day effects" parameters generally showed results suggestive of a greater subjective sense of daytime alertness and ability to function, and less morning sleepiness with ESZ treatment conditions compared to placebo, except for POMS factor score, which generally showed no significant difference between active treatment conditions and placebo. These results are shown in Tables VIC8 in the appendix (as provided by the sponsor).

Study 190-045: Sleep Architecture Results.
Table VIC9 Panel A in the appendix summarizes these results and results of Study 190-046 (a 6-week non-elderly patient trial) are also shown in Panel B of this table for comparison, a study that is described later in this review. Significant treatment group effects between ESZ and placebo on Stage 2 sleep were observed (as % total sleep time or total time in minutes), that were dose-dependent (based on numerical comparisons showing increased % or time in Stage 2 with increasing ESZ dose-levels). Significant decrease in % total time in REM was also observed with ESZ treatment compared to placebo, in a dose-dependent manner. The absolute time in

REM only showed small trends for a treatment effect with ESZ, whereas, 10 mg zolpidem treatment was associated with a significant increase in total time in REM compared to placebo.

Study 190-045: Conclusions

Pending confirmation by the biometric reviewer, Study 190-045 provides at face, positive results for a treatment group effect on sleep initiation, as reflected by the median value of LPS obtained by PSG recordings in which the value was less in each of the ESZ dose levels compared to placebo. Secondary results generally showed similar treatment condition effects.

Despite the sponsor's results, several problems exist regarding the interpretation of the results. This study was a crossover study, rather than a parallel group trial, which introduces several potential confounding variables. Results on the mean change in LPS from a baseline or placebo condition compared to an ESZ condition were not described. The rationale for statistical methods described in the study report is not clear, but this is primarily a Biometric issue.

Another potential problem with interpreting data in this trial is that unpleasant taste was reported that was ESZ treatment-related (lower incidence or no reports in placebo and zolpidem conditions) and was ESZ dose-dependent. These results were revealed despite that subjects only had a single dose over a 2 night period in a given treatment condition and despite the limitations inherent with a cross-over design. Consequently, a major concern is that blinding methods to the study drug may not be adequate in this trial.

The issue of a compromised double-blind study design is of greater concern in other trials in which unpleasant taste was reported in approximately one-third of subjects at the recommended therapeutic dose-level of 3 mg in subjects of the multiple-dose, non-elderly Chronic Insomnia trials, as described later.

2. Study 190-046

Study 190-046 was very similar to the previously described study (Study 190-045) except for a few major differences in the study design. Study 190-046 used a parallel group design, rather than a cross-over design. The trial was employed a longer duration of double-blind treatment (44 days of nightly-bedtime treatment) allowing for the examination of potential tolerance to treatment effects on sleep parameters. Furthermore, this trial included a two-day washout phase following double-blind treatment to examine potential rebound effects on PSG and other sleep parameters upon abrupt treatment cessation. However, proposed efficacy claims were based on PSG data last obtained on Day 29 of double-blind treatment (4-weeks of treatment). Hence, the sponsor's proposed efficacy claims do not apply to a full 6-week treatment period.

Study 190-046: Objectives

As with the previously described study (Study 190-045), the primary objective of Study 190-046 was to show efficacy of ESZ compared to placebo in the treatment of Chronic Insomnia in nonelderly adult patients using objective LPS (as determined by PSG) as the primary efficacy variable (PSG recordings were conducted on Days 1, 15 and 29 of treatment).

Secondary objectives of the study included an examination for potential tolerance or rebound effects, and potential effects on subjective ratings of daily functioning associated with 44 consecutive days of daily ESZ treatment compared to placebo.

Study 190-046: Study Design and Subjects

This study is a multicenter, randomized, placebo-controlled, PSG and outpatient study employing a parallel group design and a 44 day double-blind treatment phase. A total of 308 generally healthy adults (between ages 21 to 64 years old) with Chronic Insomnia (by DSM-IV criteria) were randomized to one of the following treatment groups (in a 1:1:1: ratio):

- Placebo group: 3 tablets po Qhs (at bedtime with 240 ml of water).
- 2 mg ESZ group: 2 ESZ tablets (1 mg/tablet) and 1 placebo tablet p.o. Qhs (at bedtime with 240 ml water).
- 3 mg ESZ group: 2 ESZ tablets (1.5 mg/tablet) and 1 placebo tablet p.o. Qhs (at bedtime with 240 ml water).

Double-blind treatment was for a period of 44 days. The lot numbers of ESZ tablets used for this trial were identical to those used in Study 190-045. The eligibility criteria used in both studies were also almost identical. Refer to the corresponding section for Study is 190-045 for details on eligibility criteria and prohibited medications.

A 2-night single-blind placebo lead-in phase (Visit 1) preceded the double-blind treatment phase. Unlike other efficacy trials, a post-treatment wash-out phase of the study was employed, following the double-blind treatment phase and involved a 2-nights of single-blind, placebo treatment (on Visit 6 corresponding to the nights of study Days 45 and 46). Nights 45 and 46 are also referred to as Rebound Nights 1 and 2 or R1 and 2.

PSG recordings were conducted on the two consecutive nights of each of the Placebo Lead-in and Washout phases. The lead-in phase allowed for PSG screening of the subjects to determine if they met PSG eligibility criteria, similar to the methods and criteria used for Study 190-045 (except that PSG recording was for only two, rather than three, nights of bedtime placebo dosing and PSG recording). The 2-day Washout phase allowed for examination of potential rebound effects on PSG and other sleep measures upon cessation of treatment in the double-blind phase. Subjects completed Morning Questionnaires on the mornings of the last two days of double-blind treatment (Days 43 and 45) before undergoing the 2-night washout phase (Visits 6).

PSGs were also conducted at various time points during the double-blind treatment phase, as described in the following. Subjects were instructed to return to the study site within 2 to 5 days after the lead-in phase, to undergo two nights of PSG recordings (Visit 2). Subjects received single-blind placebo on the first night of Visit 2 (data that was collected on this night, as well as in the following morning, served as baseline data for the rebound effects analyses, described later). On the second night of Visit 2 subjects received their first dose of their assigned study drug (refer to as Day 1). Subjects returned to the study site for additional PSG recordings during the double-blind treatment phase on Days 15 and 29 (Visits 4 and 5) of treatment. It should be noted that the final on-treatment PSG recording was conducted on the night of Day 29 corresponding to a period of 29 days of nightly treatment, rather than on the last night of double-blind treatment. According to the study report in the submission, the original protocol included a Visit 3 for PSG recording during the double-blind treatment phase of the study (the time point for Visit 3 was not specified in the submission). However, Visit 3 was later deleted in a protocol amendment dated February 28, 2001 (as described on page 51 of the 190-046.pdf file; the study report file). The rationale for this protocol amendment could not be found in the submission.

Safety and efficacy assessments were almost identical to those employed in the previously described study (Study 190-045) and were conducted according to the Schedule Study Assessments shown in Table VIC10 in the appendix (as provided by the sponsor). Unlike Study

190-045, the present study, 190-046, included the Digit Symbol Substitution Test (DSST), which was conducted between 9.0-9.5 hours after the previous night dosing (corresponds to 1 to 1 ½ hours after morning awakening). Romberg and Heel-to-Toe test were also conducted during this time period, as in Study 190-045. As shown in Table VIC10, monitoring of subjects continued during the washout phase and final safety assessments occurred between five to seven days after the last dose of study drug. Morning Questionnaires were completed on each study Visit (in the sleep laboratory) and Evening Questionnaires were conducted in the sleep laboratory on study Visits, as well as at home by the subjects each night between each study visit, as shown in Table VIC10 which includes other safety assessments that were conducted.

Study 190-046: Efficacy Assessments

Primary, key secondary, and other secondary assessments are described in the study report of the submission and were generally the same as those in the previously described study (Study 190-045), in which the primary efficacy variable was LPS (as assessed by PSG). Secondary variables included subjective and objective sleep measures (objective PSG measures, sleep architecture measures, and subjective sleep ratings from the Morning Questionnaire). Tables VIC2-4 provides a listing of efficacy and safety-related sleep measures ("Next Day Effects" measures from the Evening Questionnaire and the POMS) and for definitions of each variable used in Study 190-045 that are generally the same as those employed in Study 190-046.

Study 190-046: Statistical Analysis of Primary and Secondary Variables

The ITT population dataset was used for the primary analysis and most of the secondary analyses. The primary efficacy variable was LPS (in minutes) over the double-blind treatment phase (the mean of LPS on Visits 4, 5 and 6). As in Study 190-045, the data was ranked-transformed and an ANOVA model with treatment and site as fixed effects was employed. However, unlike Study 190-045, the present study did not pool the ESZ groups for an initial ANOVA analysis. Instead, the primary analysis in the present study, was a comparison between the 3 mg ESZ group to placebo using the ANOVA model (with $\alpha = 0.05$; two-tailed). Using this same ANOVA model the 2 mg ESZ group was then compared to placebo on the primary efficacy variable, as well as on various secondary variables. Secondary comparisons between each ESZ group and the placebo group on LPS were conducted for each double-blind phase visit (Visits 2, 4, and 5).

Additional secondary analyses were conducted on both objective and subjective measures generally using the same statistical methods as for the primary analysis, unless otherwise specified in the results section (secondary analyses was conducted on PSG measures, Evening Questionnaire measures, Sleep Architecture measures and on "Next Day Effect" parameters: Morning Questionnaire and POMS scores).

It is important to note that data from 20 subjects on several secondary efficacy parameters were not included in the statistic analyses. These subjects had values on subjective sleep latency, subjective WASO, subjective total sleep measures (secondary variables) that were considered by the sponsor to be extreme (values exceeding 599 minutes). Therefore, data from these subjects on these particular parameters were deleted from the dataset analyzed for the secondary analyses. These subjects and their corresponding values are listed in Table 11.1-1 in the study report (page 55 of the 190-046.pdf study report file in the submission). The exclusion of these data from the dataset appears to be reasonable for data analysis on these variables for a number of reasons. The values exceeded 599 minutes, yet such values are not likely given the nature of the study

population (i.e. patients with Chronic Insomnia meeting specified DSM-IV and study criteria), along with the cut-off values for subjective and objective sleep measures used to determine eligibility for the study.[3] Finally, the analyses conducted on these variables were secondary or exploratory in nature.

Study 190-046: Results on Demographic Features, Exposure, Protocol Violations

Before describing efficacy results, results on demographic features, exposure to double-blind treatment and protocol deviations are described in this subsection.

Overall demographic features were described previously in Section VI.B.3, while this paragraph focuses on salient observations of these results (as shown in Table VIB11 in the appendix). The 3 mg ESZ group had the greatest incidence of female subjects (73% compared to 57 to 64% of subjects in the other group) with overall treatment group effects on the incidence by gender being significant (p=0.03). Treatment groups also showed a significant effect on mean BMI (for female and male subjects combined) but the magnitude of treatment group differences was numerically small (only 1 to 2 kg/m^2 between any given two groups).

The following description of exposure is based on results shown in Tables 14.1.5 and 14.1.6 (on pp.113 and 114 in the Study Report of the original submission, in 190-046.pdf file). Double-blind treatment compliance ranged from the 97 to 99% in mean compliance and was 100% in median compliance among the treatment groups (calculated according to methods described in the tables). The minimum compliance among the treatment groups ranged from 67% to 87%.

Using the number of tablets returned at each study visit to calculate exposure results on exposure by number of days and number of doses (number of doses was divided by 3, since subjects received 3 tablets per dose). The methods for these calculations and the results were provided in Table 14.1.6 in the study report of the original submission. As shown in this table, the mean number of days and mean number of doses of double-blind treatment for each treatment group was 43 days and 42 doses, respectively (SD ranged from 4 to 7 among the groups, the median number of days and doses was 44 days and 43 doses in each group).

The majority of subjects (66% of subjects) were identified as having "important" protocol deviations. Yet, 90% of subjects were reported as completers yet on p. 25 of CSR proto viol's resulted in DC of study. It appears from these incidence rates that "important" protocol deviators are different from protocol violators and that the former subgroup remained in the study, while the later subgroup were withdrawn from the study. It appears that a committee identified subjects as protocol deviators. This selection process is not clear to this reviewer (e.g. prespecified, a priori criteria for "important" deviations cannot be found and a priori methods regarding the analysis of the data from these subjects). The categories of these "important" protocol deviations (categorized by type of deviation) found in an end-of-text summary table showing the incidence of subjects by type of deviation showed the following results for categories in which the incidence was at least 5% in any given treatment group:

- Testing positive on the urine drug screen (including Visit 2), which occurred in approximately 6% to 7% of subjects in any given group.
- The dosing time in the sleep laboratory deviated by at least 15 minutes from the onset of PSG recording: in approximately 10 to 14% of subjects in any given group.

[3] Specified subjective sleep and PSG cutoff eligibility criteria were employed which included a requirement that subjects reported no more than 6.5 hours a sleep each night for at least one month prior to study entry.

- Caffeinated food was consumed after 1500 hrs in the sleep laboratory: in 6% to 7% of subjects within any given treatment group.
- Exceeded the three cup minimum of caffeinated beverages in any given day while in the sleep laboratory: approximately five to 9% of subjects in any given treatment group.
- A deviation in DSST administration by > 15 minutes: in 17% to 23% of subjects in any given treatment group.

One important observation is that distribution of subjects among the various categories of "important" protocol deviations was generally similar across the treatment groups for each given category (as shown in Table 14.1.2 in this study report file 190-046.pdf, starting on p. 106). Furthermore, it is noteworthy that only 3% of the ITT Efficacy population received prohibited concomitant medication.

Clarification on the above is needed to be able to draw conclusions on at least the efficacy results of this study.

Study 190-046: Efficacy Results

Tables VI C. 11-12 and Figure VI.C. 3-4 in the appendix summarizes the primary and secondary efficacy results in the results by study visit during the double-blind phase on the primary efficacy variable, LPS. Note that while the median number of minutes of LPS appears to be fairly stable over time in the two ESZ groups (on Days 1, 15, and 29 of the double-blind phase), the median LPS in the placebo group shows a gradual decline from Day 1 (Night 1) to Day 15 (Night 15) and a more dramatic decrease on Day 29 (Night 29). Nevertheless, pairwise comparisons between each of the ESZ groups to the placebo group were highly significantly different on each of these days of the double-blind treatment phase ($p < 0.001$ to $p < 0.0001$).

Results on objective Sleep Efficiency and on median objective WASO generally appear to show the greatest treatment group differences (in both the magnitude of the effect and the p value for a significant effect) for both the low and high dose ESZ groups compared to placebo on Day 1 (Night 1) compared to Nights 15 and 29. The high dose ESZ group showed more consistently, than the low dose group, a significant treatment group effect (compared to placebo) on these parameters for the overall period of the double-blind treatment phase (Days 1, 5, and 29) and by each study visit.

The median objective WASO only showed a treatment group effect in the high dose ESZ group compared to placebo for the "overall" period (averaging the data from each visit during the double-blind phase; Days 1, 15 and 29). The low dose group only showed significant effects on Day 1, and not on Days 15 and 29. Despite effects for the overall period in the high dose group, this high dose group failed to show a consistent significant treatment group effect (compared to placebo) over time (no significant treatment group effect was observed on Night 15). In fact, the numerical values for the median objective WASO on Night 15 were in the negative direction compared to placebo in each of the ESZ groups (values were numerically greater in each ESZ group than the value in the placebo group). However, numerical trends appear in the opposite direction (i.e. for a positive effect in each of the ESZ groups compared to placebo) at other time points (Nights 1 and 29) on WASO and at all time points (Nights 1, 15 and 29) on the median objective Sleep Efficiency parameter.

The results of other objective and subjective secondary sleep measures and analyses were generally similar to those observed for the primary and key secondary measures. The results of secondary measures are shown in Tables VIC12 and Figures VIC 3-4 in the appendix (showing results either for the overall, double-blind phase over Visits 1, 15 and 29 or by each of these

visits, as provided by the sponsor). However, as shown in these tables, some objective and subjective measures (primarily those variables reflecting the wake time after sleep) failed to show significant treatment group effects upon pairwise comparisons (either overall; over Visits 1, 15 and 29 or by study Visit). Some variables showed at least trends for treatment group differences (between a given ESZ group compared to placebo) in a direction that is opposite of the direction expected for a beneficial ESZ treatment effect (values reflect at least a numerically greater positive effect in the placebo group compared to either of the ESZ groups, such as the results on objective Number of Awakenings).

When significantly greater effects were observed on several of the above secondary variables in the high dose ESZ group the greatest effect or the most significant effect (upon pairwise comparison to placebo) was observed on Night 1 (compared to Nights 15 and 29, based on visual inspection of the summary tables). The low dose group showed significant treatment group effects on Night 1 but generally showed a similar pattern for a lesser effect on subsequent nights. These observations pertain to the following parameters: the primary efficacy variable (LPS), "key" secondary variables (median objection sleep efficiency and WASO), objective Wake Time After Sleep, objective Number of Awakenings, and most subjective sleep measures: subjective Number of Awakenings, subjective WASO, subjective Quality of Sleep, and subjective Depth of Sleep. These results suggest development of tolerance within the 29 Day period while noting that the sponsor only chose to conduct PSG recordings out to Day 29 rather than throughout the double-blind treatment phase in this 6-week trial (also note protocol changes of dropping a visit of PSG recording, as previously described).

Study 190-046: Unpleasant Taste Associated with ESZ

Because of concern that an unpleasant taste associated with the study drug could influence the integrity of the double-blind design of the study, the incidence of the adverse event of unpleasant taste is provided in the following for each treatment group:

- Placebo group: 3 subjects (3.0%).
- 2 mg ESZ group: 17 subjects (16.3%).
- 3 mg ESZ group: 36 subjects (34.3%).

These results show a rather marked dose-dependent and treatment group effect on the incidence of unpleasant taste (based on numerical comparisons). These observations pose a serious problem as to the integrity of the double-blind design which could be compromised to the extent of jeopardizing the interpretability of the efficacy results. A discussion regarding this potential issue cannot be found in the study report.

Study 190-046: Subgroup Analysis of Efficacy Results

Potential subgroup differences on efficacy are suggested by results described below, but are only considered preliminary and did not appear to be reproducible in other trials.

Summary tables on subgroup analyses (by age, gender and ethnicity) of the primary efficacy variable (objective LPS) by study visit (Days 1, 15, and 29) and for the overall, double-blind assessment period (the average of Days 1, 15, and 29) are provided in the study report of the original submission (Tables 14.2.7.1-14.2.7.3 starting on p. 143 in without 190-046.pdf file). As shown in these tables, the following subgroups showed similar results to those for the subgroups, combined (as described in the previous subsection). That is each ESZ group had significantly

lower median LPS than the placebo group for the overall assessment period, as well as for each study visit ($p < 0.001$ and a most every comparison):

- > 35-year-old age group.
- Female gender group.
- Each ethnic subgroup (categorized as Caucasian or Noncaucasian) .

The subgroups not listed above, generally showed a significantly lower median LPS in each of the ESZ groups compared to placebo, but for only one time point, which was Day 1 (each ESZ group generally did not show significant or in some cases, even a trend for, lower median LPS than the placebo group on subsequent study visits or for the overall assessment period). These subgroups are listed below:

- < 35-year-old age group.
- Male gender group.

The above observations for these two subgroups may be reflecting a small sample size effect (as these were smaller subgroups than their corresponding comparison subgroup and sample sizes were only approximately 40 subjects/treatment group). However, this reviewer believes that a small sample size effect on reaching a level of significant in these subgroups is unlikely for the following reasons. Firstly, both subgroups showed a consistent pattern over time that may be suggestive of a tolerance effect, yet the sample size did not vary over time (in some cases the trends were in the opposite than predicted direction). Secondly, the non-Caucasian subgroup consisted of only 33 to 36 subjects in a given treatment group, yet consistently showed significant treatment group effects over time ($p< 0.001$ for most time points). Variance in standard deviations does not seem to explain the results, as the non-Caucasian subgroup had a very large standard deviation in each of the ESZ groups on Day 29, but still showed a highly significant treatment group effect. Examination of the standard deviations in the summary tables for other subgroup analyses also failed to show any consistent pattern that might explain the above observations.

One possibility that needs consideration is the possibility that the male subgroup could consist of primarily subjects who are < 35 years old and that the above observations are real, rather than due to an artifact. Another consideration is that the above results represent a real direct or secondary effect on both age and gender on treatment group effects of LPS over time (also consider a possible interaction effect). For example consider the possibility that the subgroup differed in the incidence of subjects with unreported ethanol/substance abuse disorders (as a positive urine drug screed was a common protocol deviation in subjects of the trial). Also consider undiagnosed sleep apnea which is more common in older men. Consider menopausal status effects on sleep. Also consider differences in BMI. In conclusion these comments can only be considered speculative, as the study was not designed to focus potential subgroup effects. Also the above observations did not appear to be reproducible in other trials.

Study 190-046: Results on Next-Day Effects

Unlike, PSG and several other sleep assessments, assessments for "Next-Day effects" were conducted throughout the 6-week double-blind phase. Figure VIC5 in the appendix shows results on parameters obtained from the Evening Questionnaire for each week of the 6-week double-blind treatment phase (Daytime Alertness and Daytime Ability to Function, as provided by the sponsor). In summary, only the high dose ESZ group showed significantly greater median

scores on each of the two parameters during week 2, but not on the other weeks. However, there were small trends for greater median scores over increasing dose-levels on each parameter on each week during the double-blind phase (based on numerical comparison between the 2 mg and 3 mg ESZ groups). Trends for greater median scores of each ESZ group compared to placebo were also observed on each week of the double-blind treatment phase (based on numerical comparisons between each of the ESZ groups compared to placebo). The results on the POMS generally failed to show remarkable or significant treatment group differences between each ESZ group compared to placebo.

Despite the above results on Daytime Alertness and Daytime Ability to Function, results on the Morning Sleepiness parameter obtained from the Morning Questionnaire revealed trends for higher scores (greater morning sleepiness) in each of the ESZ groups (median score of 51 mm in each group) compared to placebo (in median score of 48 mm). However, these group differences between each ESZ group and placebo were small magnitude and failed to reach a level of significance.

Study 190-046:DSST Results. The sponsor describes DSST results under the safety section of the study report. It is not clear to this reviewer why performance on the DSST was not considered a "next-day effects" parameter. Table VIC13 (in the appendix) summarizes the results (as provided by the sponsor). A rationale for using ranked transformed data for statistical analysis for a treatment group effect could not be found in the study report. Upon examination of the results in this table, the mean or median scores (or the change from baseline in mean or median scores) generally showed a numerically increase in value over time in each treatment group (baseline, Days 1, 15, 29, and on both rebound days, combined; Days 45 + 46). These results suggest a learning effect over time, independent of treatment. Despite a potential learning effect the following treatment group showed trends for greater impairment in ESZ groups compared to placebo were observed. The 2 mg ESZ group has numerically lower values than the placebo group on the last assessment in the double-blind phase (Day 29) and the 3 mg ESZ group has numerically lower values than the placebo group at almost all time points.

The absence or diminished learning effect in ESZ groups relative to placebo needs consideration in the interpretation of DSST results, as the results could reflect a greater adverse effect of the study drug compared to placebo, that is not apparent in the statistical methods employed by the sponsor.

Study 190-046:Sleep Architecture Results. Results are generally similar to those observed in Trial 190-045, as shown in Table VIC9B in the appendix.

Study 190-046: Results on Rebound Effects

Results of Rebound Effects on Efficacy Variables Figure VIC6 (in the appendix) provides results on median objective LPS, sleep efficiency and WASO at baseline and on each study Visit during the double-blind treatment phase (Nights one, 15, and 29) and the washout phase (Nights 45 and 46 or referred to as Rebound Nights 1 and 2), as provided by the sponsor. Results are also shown in tabular form in Table VIC14 (in the appendix). These tables show the mean and median change from baseline (the baseline night of Visit 2, prior to double-blind treatment) to each rebound in night (Nights 45 and 46) and results of various statistical analyses (as provided by the sponsor).

As shown in the summary tables, statistical comparisons between each ESZ group and placebo, generally failed to consistently reach a level of significance (particularly in the high dose group) on the median change from baseline to the 2-night rebound period (when averaging results from both rebound nights)[4]. However, significant treatment group differences were generally revealed on the first rebound night on the median or mean change in values from baseline. These results revealed that the low and high dose ESZ groups consistently showed a numerical worsening of objective sleep efficiency and WASO from baseline to the first rebound night (the first night after double-blind treatment cessation). It is also notable that this worsening (on each of these parameters) was numerically greater on Rebound Night 1 (Night 45 of the study) compared to Rebound Night 2 (Night 46). If these observations in the ESZ group were due to lack of efficacy, one would not expect that this worsening would abate or diminish on the second rebound night. Note that in the placebo group, not only showed a numerical or significant improvement from baseline to each of the two rebound nights, but also, this numerical improvement was greatest on Rebound Night 2 (compared to Rebound Night 1).

The above observations of a potential rebound effect can be more easily seen upon examination of Figures VIC6, while noting a rather marked worsening in each parameter between Day 29 of the double-blind treatment phase to Rebound Night 1 (corresponding to Night 45 in the figures) that is numerically greater in the high dose ESZ group, while the placebo group either shows no change or trends for greater improvement between these same sleep laboratory nights. Furthermore, the 2 mg ESZ group shows values on each rebound night (Nights 45 and 46 in the figures) that are numerically different (worse) than the values at baseline (Table VIC14 shows significant differences in the 3 mg ESZ group for some of the variables). The placebo group either showed numerically greater improvement or no change in these parameters compared to baseline.

Rebound Effects Sleep Architecture. PSG recording were conducted on the two Rebound Nights, yet results on sleep architecture on these nights could not be found in the study report.

Rebound Effects on AEs (Withdrawal AEs) in Study 190-046

Treatment groups (placebo; n = 99, 2 mg ESZ, n = 104, 3 mg ESZ, n = 105) were generally similar on the incidence of withdrawal AEs (total AEs and in each AE category). The incidence of withdrawal AE's (AE's for all categories, combined) was 8%, 8%, and 9%, in the placebo, 2 mg, and 3 mg ESZ groups. The incidence of each category of AE's was less than 2% in any given treatment group with the exception of Nervous System AE's: 2%, 1.9%, and 2.9% in the placebo, 2 mg, and 3 mg ESZ groups. Among nervous system AE's in the ESZ groups or the following (the incidence in placebo, 2, mg 3 mg ESZ groups are shown):

- Abnormal dreams: 0%, 0%, to 1.9%
- Anxiety: 0%, 1.9%, 1.0% .

The above AE's reflect those that were reported on the first single-blind placebo day at Visit 6 or within 48 hours or between 24 to 48 hours after the last dose in subjects who withdrew early from the study.

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[4] As described in the summary in the appendix, the change from baseline and sleep parameters was analyzed using the Wilcoxon Signed Rank test. Pairwise comparisons were conducted with rank-transformed change from baseline data using an ANOVA model with treatment and site as fixed effects.

Study 190-046: Conclusions
Overall the results as presented by the sponsor show a significant treatment group effect on several variables including the primary efficacy variable, but the greatest effects appear to be on Night 1. Consistent with a possible development of tolerance to efficacy effects over time are the results on the rebound nights, that evidence suggestive of rebound effects. Rebound effects of EEG could not be found in the submission. The results on withdrawal AEs showed minimal to no rebound effects on the incidence of AEs.

A major concern in the interpretability of these results is a marked dose-dependent effect on the incidence of unpleasant taste that occurs in one third of subjects at the recommended dose level in proposed labeling.

Another major concern is regarding a subgroup of subjects identified as "important protocol" deviators, as previously described. As the methods employed and the actual data included in at least the analysis of efficacy data can impact on what conclusions may be drawn from the results, as presented by the sponsor and the ability to interpret the results.

Adverse effects of ESZ on DSST performance is also suggested by the results of this trial. Consideration also needs to be given to potential drug effects on practice effects over time, as previously described.

3. Study 190-049
Study 190-049: Objectives
The primary objective of this 12-month trial was to examine long-term safety of ESZ treatment (3 mg taken orally, each night at bedtime) using a placebo controlled design during a 6-month double-blind treatment phase that was followed by a 6- month open-label ESZ phase (3 mg po Qhs).

The study report in the original submission specifies that the examination of efficacy (using subjective sleep measures) in patients with Chronic Insomnia was a secondary objective of this trial (using subjective sleep latency as the primary efficacy variable).

Study 190-049: Study Design and Subjects
This trial is a multicenter (70 sites), parallel group, fixed dose, long-term outpatient trial using subjective efficacy measures. A 6-month double-blind phase was followed by a 6-month open label ESZ phase (3 mg of ESZ Qhs at bedtime). 791 eligible subjects (21-64 years old, generally healthy men and women, with Chronic Insomnia by DSM-IV criteria) were randomized to one of the following two treatment groups:

- Placebo group: 2 tablets po Qhs (at bedtime).
- 3 mg ESZ group: 2 tablets po Qhs (either two 1.5 mg tablets or one 1 mg tablet and one 2 mg tablet, taken at bedtime).

Subjects were instructed to have dinner at least two hours prior to their bedtime dosing. Subjects were required to take at least 3 daily bedtime doses per week or 15 daily bedtime doses per month to remain in the study (compliance was assessed at each monthly study visit using the

number of tablets returned minus the number of tablets missing or stolen, divided by two tablets/dose).

Subjects who completed the six month double-blind treatment phase were eligible to enter into a 6-month ESZ open-label phase. A total of 471 ITT efficacy subjects participated in this phase. During the open-label phase all subjects were instructed to take one tablet (a 3 mg ESZ tablet) orally every night at bedtime.

Lot numbers of the placebo, 1 mg ESZ, and 2 mg ESZ tablets used in the previously described trials were the same as those employed in Study 190-049. However, two additional lot numbers of ESZ tablets were used in this longer term trial (corresponding to the 1.5 mg and the 3.0 mg tablets).

Subjects underwent clinical assessments for screening on Visit 1, according to the Schedule of Assessments Table VIC15 in the appendix (as provided by the sponsor). A maximum screening period of 14 days was employed to determine eligibility. Eligibility criteria used in the trial were generally similar to those employed in Study 190-046. Women were permitted to use hormonal therapy and hormonal contraceptive agents (women considered as not having childbearing potential were those who were surgically sterilized or who had post-menopausal amenorrhea for at least one year). Hepatitis B and C screening was employed and subjects who participated in any investigational study within 30 days prior to the screening visit were excluded from the study.

The following outlines some key differences in eligibility criteria used in Study 190-049 that were generally not employed in other Chronic Insomnia studies:

- Eligibility criteria of self-reported sleep patterns differ somewhat from other Chronic Insomnia Trials. In other trials, subjects meeting DSM-IV criteria for Chronic Insomnia also had to report **both** of the following sleep characteristics, while in this longer term trial (190-049) subjects (who also had to meet DSM-IV criteria for Chronic Insomnia) only had to meet **either** of these criteria on self-reported sleep patterns (during at least one month prior to the study):
    - Reports no more than 6.5 hours a night of sleep **and** (as stated in previous Chronic trials), "**and/or**" (as stated in Section 9.3.1 of the Study Report of Study 190-049)
    - Takes more than 30 minutes to fall asleep at each night over the previous month.
- In previously described trials, subjects were excluded if they had previously participated in an ESZ trial, while in Study 190-049 subjects were excluded if they participated in a trial within 30 days prior to screening.

Another unique feature of the eligibility criteria in Study 190-049 that was not employed in other trials involved screening subjects for cancer (as other trials were short-term trials):

- Subjects with "history of, or current malignancy except for non-melanomatous skin cancer" were excluded from Study 190-049.
- More restrictive screening criteria were employed regarding subjects with active thyroid disease, women "considered at risk for breast cancer," and "all subjects at risk for lung cancer." These additional, unique, eligibility criteria could not be found in the listing of inclusion and exclusion criteria in Sections 9.3.1 and 9.3.2 of the study report. Instead, the criteria were found in a section describing procedures for Visit 1 (Section 9.5.1.1 of the study report). The following text was taken from this section of the study report:

- *Documentation of a negative mammogram was required within the past 12 months for all females considered at risk for breast cancer. If documentation of a negative mammogram was not available, the subject was not eligible for the protocol. A mammogram was not provided or paid for by the sponsor for the purpose of participating in this protocol.*
- *Documentation of a negative thyroid scan in the past 12 months was required for all subjects with evidence of active thyroid disease. If documentation of a negative thyroid scan was not available, the subject was not eligible for the protocol. A thyroid scan was not provided or paid for by the sponsor for the purpose of participating in this protocol. Exceptions were made on a case-by-case basis for subjects receiving thyroid replacement therapy at a stable dose for at least 3 months.*
- *Documentation of a negative chest x-ray in the past 12 months was required for all subjects at risk for lung cancer. This included subjects with significant (per Investigator's discretion) exposure to asbestos, and those with more than 1-pack per day for a year (1 pack-year) of cigarette smoking. If documentation of a negative chest x-ray was not available, the subject was not eligible for the protocol. A chest x-ray was not provided or paid for by the sponsor for the purpose of participating in this protocol.*

The following outlines the study visits, including a brief description of the procedures for each visit (refer to Table VIC15 in the appendix for details on the assessment schedule):

- **Baseline Visit (Visit 2)**: eligible subjects were randomly assigned to double-blind study drug and underwent safety assessments according to the schedule shown in Table VIC15.
- **Double-blind Phase (Visits 3-8):** these visits occurred monthly (±5 days) while subjects were receiving their double-blind treatment. Safety and compliance assessments were obtained and subjects received their monthly refill of study drug at each of these visits.
- **Open-Label Phase (Visits 9-14):** these monthly visits (±5 days) occurred over the open-label phase of the study and involved similar procedures to those employed on visits during the double-blind phase (as shown in Table VIC15).
- **End-of-Study Visit (Visit 15):** subjects were to return within approximately one week after their last dose of study drug (within 5-7 days post-dose) and underwent final assessments, as shown in Table VIC15.

In addition to assessments shown in Table VIC15, women were inquired about their menstrual history and use of hormonal therapy at each monthly study visit.

The protocol was amended (in Amendment 3) to only include vital sign measures that were obtained while seated (orthostatic measures were deleted, as described in the study report of the submission). The rationale provided for deleting orthostatic measures during vital sign assessments was that measures were being obtained at time points near minimal or trough levels (as described on pp.62-63 of this study report 190-049.pdf file).

Study 190-049: Efficacy Assessments

Primary and secondary assessments were obtained from the Evening Questionnaire using an Interactive Voice Response System (IVRS). Subjects completed a questionnaire via IVRS on a

weekly basis throughout treatment. Subjects were to complete the questionnaire in the evening on the same day of each week (±1 day).

The primary efficacy variable was sleep latency (in minutes), which was defined as the subjective average time to fall asleep over a given week. Table VIC16 in the appendix provides a listing of the efficacy variables and each corresponding definition (as provided by the sponsor).

According to the study report the key secondary variable was the mean total sleep time over the last three months of the double-blind treatment phase.

Study 190-049: Statistical Analysis of Primary and Key Secondary Variables
The mean of the monthly averages over the last three months of the double-blind phase on sleep latency was determined for the primary efficacy variable (the mean of the monthly averages for months 4, 5 and 6). Secondary analysis was conducted on the monthly averages on sleep latency throughout the double-blind phase.

The following describes how missing values were handled in calculating monthly mean sleep latency values. The LOCF approach was used for calculating each monthly average (at least two values in a given month were required to calculate the monthly mean value). At least two values in a given month were required to calculate the monthly mean value, while the following describes methods when only one value existed on a give month. If only one value existed for the first month, then the first month mean value was considered missing. On subsequent months, if only a single value existed for given month, then the value was summated with the mean value of the previous month, divided by two, to obtain that given month's average (as described on p.51 in the 190-049.pdf file). These methods were also generally employed for determining results by each month on each secondary variable.

An ANOVA with treatment and site as fixed effects was conducted to compare the 3 mg ESZ group to placebo on the primary efficacy variable. The data was ranked-transformed for this analysis. This same approach was generally used for the statistical analysis of each secondary variable, unless otherwise specified in the results section of this review.

Study 190-049: Results on Demographic Features, Exposure, and Protocol Violations.
Subject disposition, demographic features and exposure are described elsewhere in this review. This section focuses on salient features regarding these aspects of the study population.

Almost 100% of the randomized subjects were in the ITT population of the double-blind treatment phase of the study. Approximately 60% of randomized subjects completed the 6-month double-blind treatment phase of the trial. The distribution of subjects within each disposition category was generally similar across treatment groups in the double-blind treatment phase, with the following exceptions. Approximately 13% of the ESZ group discontinued double-blind treatment due to an adverse event compared to only 7% of placebo subjects. The placebo group had almost twice the incidence of subjects who voluntarily withdrew from the study compared to the ESZ group (26% of placebo subjects compared to only 14% of ESZ group). Only approximately 3% of subjects withdrew from the study due to a protocol violation.

A total of 471 subjects were in the ITT efficacy population. Approximately 81% of these subjects completed the open-label treatment phase of this study. Refer to Table IV.B.1.b. in Section IV of this review for further details on the enumeration of subjects in a given population and treatment group. This table also provides a number of subjects who received a total of six

months or 12 months of ESZ. Only 4% of the ITT population withdrew prematurely due to an adverse event during the open-label treatment phase of the study.

Treatment groups were generally similar in demographic features (mean or median age and height) and in the distribution of subjects across gender or ethnic categories. However, the ESZ group had a significantly greater mean weight (by 5 kg) and BMI (by only approximately 2 kg/m^2) than the placebo group of the double-blind treatment phase.

Tables 17-20 in the appendix provide results on the exposure of subjects during the double-blind treatment and open label phase in addition to overall exposure to ESZ treatment throughout both phases of the study. Approximately 50% of ESZ subjects received a mean daily dose of at least 2.75 mg and approximately 50% of placebo subjects received treatment over a period exceeding five months during the double-blind treatment phase (a mean of 2.75 tablets/day in the placebo subjects and 2.75 mg/day in ESZ subjects). Approximately 12% of ESZ subjects received a daily mean dose of at least 2 mg over this time-period during the double-blind treatment phase. The results on exposure during the open-label phase revealed generally similar observations on the incidence of subjects within each mean daily dose category (mean daily dose categories of $\geqslant$ 2 mg or $\geqslant$ 2.75 mg over a period of at least 5 months). The mean compliance within each treatment group during the double-blind phase and open label phases was approximately 95% (the number of tablets taken, divided by the number of tablets to be taken). Over 43% of the subjects were within 100 to 119% range of compliance during the double-blind (in each treatment group) or open label phase.

Approximately 35% of subjects in each treatment group of the double-blind treatment phase deviated from the protocol. Common protocol deviations (at least 5% of subjects within any given group) were the following:

- Did not meet eligibility criteria (approximately 6% of subjects in each group).
- Reported a sleep history of < 16 minutes of sleep latency (8-9% in each group).
- Tested positive on the urine drug screen (5-6% per group).

Despite these common protocol deviations, the distribution of subjects across treatment groups within any given protocol deviation was generally similar.

Study 190-049: Efficacy Results

Results on the Primary Efficacy Variable. As shown in Table VIC21 in the appendix (as provided by the sponsor) the ESZ group had a significantly shorter subjective sleep latency than placebo (averaging values over months 4-6 of the double-blind treatment phase, using rank-transformed data for the statistical analysis). This table also shows secondary results on the primary variable at other time-points of the double-blind treatment phase (mean and median values over months 1-3 and by each month of the 6-month phase). These results show highly significantly shorter subjective sleep latency values (median values, ranked-transformed data) consistently over each month of the double-blind treatment phase.

See Figure VIC7 in the appendix showing the results on median subjective sleep latency for each treatment group over time, for each month of the double-blind and open label treatment phases (as provided by the sponsor).

Results on "Key" Secondary and Other Variables .

The sponsor refers to subjective total sleep time over months 4-6 (the mean of the monthly values, data ranked-transformed) as the "key" secondary efficacy variable. Table VIC22 in the appendix shows the results of this secondary variable. Also shown in Table VIC22 are results of

subjective total sleep time averaged over months 1-3 and by each month of the double-blind treatment phase (as provided by the sponsor). Significant treatment group effects for a greater median subjective total sleep time in the ESZ group compared to placebo was revealed with each pairwise comparison (over the first 3 months or the last 3 months of the double-blind phase or by each month over the 6 months). Figure VIC8, also shows these results, as well as results during the 6-month open label phase of the study (as provided by the sponsor).

Similar observations were generally revealed for other secondary variables including the subjective WASO, subjective number of awakenings, subjective quality sleep, and subjective number of nights awakened per week, as shown in Table VIC23 and Figures VIC9-VIC12 in the appendix (as provided by the sponsor).

Results of Subgroup Analyses.
Subgroup analyses were performed on the basis of gender and ethnicity on the primary efficacy variable and on the "key" secondary variable (subjective sleep latency and subjective total sleep time, respectively). Despite, some subgroups having small sample sizes either significant treatment group effects or trends for a treatment group effect were still revealed in each subgroup on these efficacy parameters (averaging values from the first 3 months or from the last 3 months of the double-blind phase).

Results on the Incidence of Unpleasant Taste
Given that unpleasant taste associated with the active drug could impact on the integrity of the double-blind design the following describes the incidence of subjects reporting "unpleasant taste."

During the double-blind phase 10 ESZ subjects (out of 593 total ESZ subjects) and no placebo subjects (out of 195 total placebo subjects) dropped out of the study due to unpleasant taste. The incidence of unpleasant taste reported as an AE in this phase of the study was 26% of subjects in the ESZ group compared to only 5.6% of placebo subjects during this phase (ITT Efficacy Population).

During the open label phase 7% of the subjects reported unpleasant taste (32 total subjects). The majority of these subjects who reported unpleasant taste in the open-label phase (22 out of the 32 total subjects) had previously received placebo during the double-blind phase.

20% of subjects who were previously on placebo reported unpleasant taste during the open-label phase of the study (out of 111 subjects in the ITT Efficacy Population for the open label phase). Only 3% of subjects who were previously assigned to double-blind ESZ reported unpleasant taste during the open label phase.

Study 190-049: Results on "Next Day" Parameters
The following results are on subjective daytime ratings. The results on daytime alertness, daytime ability to function, and sense of physical well-being, are shown in Figure VIC13 in the appendix (as provided by the sponsor). These parameters were obtained on a weekly basis in the evening using IVRS. Significantly greater values (greater benefit) were obtained in the ESZ group compared to placebo at each month of the trial throughout the double-blind and open label treatment phases (refer to the figures for details). However, the treatment group differences were very small and were consistently less than 1 unit on a 10 unit scale for each of these parameters at each of these time points (0 = very sleepy or poor and 10 = wide awake or excellent, for

daytime alertness and ability to function ratings, respectively). The results on the number of days of napping and on nap time failed to show even trends for a greater benefit with ESZ compared to placebo for virtually all the time points throughout the study. However, subjects generally reported one day to less than one day of napping (perhaps reflecting a floor effect). The mean or median number of hours of napping was approximately 27 to 30 minutes or approximately 40 minutes, respectively, at each monthly time point throughout the study in each of the groups.

This study did not include DSST assessments.

Study 190-049: Conclusions
Based on the results described in this study report for Study 190-049 the sponsor shows significant treatment group effects for greater benefit in the ESZ group compared to the placebo group on the primary efficacy variable and the "key" secondary variable (subjective sleep latency and subjective total sleep time, respectively, with values averaged over the last three months of double-blind treatment, ranked-transformed data). Generally similar results were observed for other secondary variables. Secondary analysis over time generally revealed similar results at each time point throughout the double-blind and open label phases (by monthly visits).

While, significant treatment group effects were revealed, almost one third of the ESZ group compared to only 5.6% of the placebo group reported unpleasant taste. Furthermore, 20% of subjects who were previously on placebo reported unpleasant taste in the open label phase when treated with the active drug compared to only 3% of open-label subjects who previously receiving double-blind ESZ. These results are consistent with unpleasant taste being associated with the active drug and present a problem in interpreting efficacy results. Consequently, the trial is not adequately designed to establish efficacy, in the opinion of this reviewer.

Because of significant group differences on BMI and weight, consideration should be given to the potential influence on these variables on efficacy results. However, group differences were small.

Significantly higher scores in the ESZ group compared to placebo were described for subjective ratings on daytime alertness and ability to function (in the direction of greater alertness and function in the ESZ group). However, these group differences were very small (less than one unit on and 10 unit scale for each of these parameters) and the level of significance was not corrected for multiple comparisons. These small differences are not in the opinion of this reviewer, clinically significant and are not adequate to establish greater daytime alertness and function with ESZ treatment. No treatment group differences were observed on subjective parameters on napping. Finally, the study did not employ any objective assessments for potential "next-day" effects (e.g. DSST, assessment of alertness).

D. Elderly Chronic Insomnia 2-Week Trials (Studies 190-047 and 190-048)
Objectives, Study Design and Efficacy Results of Studies

1. Studies 190-047 and 190-048
Study 190-047 and -048 Objectives.

Both of these 2-week trials had the primary objective of examining efficacy and safety of fixed daily bedtime doses (1 mg or 2 mg) of ESZ compared to placebo in elderly (65 to 85-years old) patients with Chronic Insomnia. Study 190-047 employed PSG efficacy measures, while Study 190-048 employed subjective efficacy measures.

Studies 190-047 and -048: Study Design and Subjects

Subjects. Both studies were conducted on 65 to 85-year-old generally healthy adults with Chronic Insomnia by DSM-IV criteria using eligibility criteria that were similar to the criteria employed for the short-term trials conducted on nonelderly patients with Chronic Insomnia (Studies 190-045 and 190-046). The total number of randomized subjects in Study 190-047 and Study 190-048 was 292 subjects and 231 subjects, respectively. PSG screening-eligibility criteria were similar to those employed in other PSG trials. Subjects could not have active thyroid disease, but subjects taking a stable dose of thyroid replacement hormone for at least three months were eligible to participate in the study.

Subjects could not have a history of, or current, malignancy except for non-melanoma this skin cancer (as required in the other short-term trials). The more stringent cancer-related criteria (involving the lung, breast or thyroid) that was employed in the longer term study (Study 190-049) was not employed in any of the shorter-term trials, including trials on elderly patients. However, unlike Study 190-049, the elderly trials excluded patients with severe chronic obstructive pulmonary disease.

Study Design. Both elderly trials were multicenter, randomized, double-blind, placebo-controlled, two-week trials employing a fixed-dose, parallel group design. Both studies had a 2 mg ESZ group (2 mg Qhs at bedtime) and a placebo group in which subjects took their bedtime dose every night throughout the 2-week double-blind treatment phase. Study 190-048 had an additional ESZ treatment group that received a 1 mg bedtime dose each night over the two weeks. Study 190-047 initially had a 1.5 mg ESZ group that was later dropped from the protocol, since similar efficacy results were anticipated between the 1.5 mg and the 2 mg dose levels. A total of 28 subjects were randomized to the 1.5 mg dose level at the time of this protocol amendment (these subjects continued in the trial). Efficacy data from this aborted ESZ group were not included in the submission.

A major difference between the two elderly trials was that Study 190-047 employed PSG measures, while Study-048 employed subjective IVRS sleep measures.

Tables VID1 and VID2 in the appendix show the overall schedule assessments in study visits in each respective trial.

Study visits for Study 190-047 (the PSG trial) were as follows:

- **Visit 1 (Screening Visit, 2-Nights of PSG Screening and Single-blind placebo treatment):** subjects underwent screening assessments and two consecutive nights of PSG screening with bedtime single-blind placebo treatment given each night, during this PSG screening visit. Subjects were to have completed a sleep log for 7-10 consecutive days prior to this visit to determine the median bedtime of each subject (lights-out).
- **Visit 2 (Nights 1 and 2):** subjects underwent PSG monitoring for two consecutive nights in the sleep laboratory and started their first dose of double-blind treatment at bedtime on Night 1. Subjects were randomized to a treatment group: placebo, 1.5 mg or 2 mg ESZ groups (in a 1:1:1 ratio). As previously described, the 1.5 mg ESZ dose-level was

aborted after randomization of 28 subjects to this group. Visit 2 was to occur within 21 days after Visit 1.

- **Visit 3 (Nights 13 and 14):** subjects underwent PSG monitoring for these two consecutive nights, which corresponded to the last two nights of the 2-week double-blind treatment phase.
- **Visit 4 (End-of-Study Visit):** subjects underwent final safety and IVRS assessments on this visit, which was to occur within 5-7 days after completing the double-blind treatment phase.

Subjects also completed IVRS subjective assessments each morning and evening, starting on Visit 1 and continued completing these assessments throughout the remainder (the last assessment was on the morning of Visit 4).

Study visits for Study 190-048 (the subjective sleep IVRS trial) were as follows:

- **Visit 1 (Screening Visit):** subjects underwent screening assessments on this visit.
- **Visit 2 (Baseline Visit):** subjects underwent additional screening assessments and safety assessments on this visit. Subjects began IVRS assessments in which they were instructed to make their IVRS calls every morning and evening throughout the remainder of the study. Visit 2 was scheduled within 14 days after the screening visit.
- **Visits 3 and 4 (Weeks 1 and 2 of Double-blind Treatment):** Visit 3 was to occur on Day 8±1 of double-blind treatment and Visit 4 was to occur on Day 15-17, which corresponds to 1-3 days after completing the double-blind treatment phase. Subjects underwent various safety assessments during these visits, as well as continuing their IVRS assessments. Visit 4 was the final study visit for safety assessments.

Studies 190-047 and 190-048: Efficacy Assessments and Statistical Analysis Methods
These trials employed virtually the same subjective or objective primary, "key" secondary, and additional secondary variables, as employed in other trials of nonelderly Chronic Insomnia patients. The following outlines these parameters for each study.

<u>Co-primary and "Key" Secondary Variables in the PSG Study 190-047:</u>

- Co-primary variables-
  - **Objective LPS** was a primary efficacy variable.
  - **Objective Sleep Efficiency** was a coprimary variable in this trial, rather than this variable being selected as a "key" secondary variable, as in the nonelderly PSG trials (190-045 and 190-046).
- "Key" Secondary Variable:
  - **Objective WASO** was a "key" secondary variable, as in the nonelderly PSG trials.

Refer to Tables VIC3-4 which provide the definitions of various efficacy variables employed in Study 190-045, which are generally similar to those employed for Study 190-047.

Data from the ITT population on the 2 consecutive PSG nights of the each visit (Visits 2 and 3) during the double-blind phase were averaged (referred to as Nights 1 and 14, respectively). This data was used for the primary analysis on each co-primary and "key" secondary variable. The data was rank-transformed and an ANOVA model with treatment and sites as fixed effects was employed to determine if significant treatment group effects could be revealed between the 2 mg ESZ and placebo groups on each efficacy variable. If each coprimary

variable showed a significant treatment group effect at the 5% significance level (for each variable), then the sponsor proceeded to conduct the same analyses on the "key" secondary efficacy variable (objective WASO).

Primary and "Key" Secondary Variables in the Subjective IVRS Sleep Study 190-048 (subjects called the IVRS to provide a subjective response to questions for each subjective sleep parameter):

Primary Variable:

- Subjective sleep latency (minutes): the subjective time after lights out until sleep onset (as assessed each morning, after arising via IVRS). Subjective sleep latency was also the primary variable in the longterm subject sleep study in non-elderly patients (Study 190-049).

"Key" Secondary Variable

- Subjective total sleep time (minutes): the subjective total duration of the sleep using data collected in the mornings via IVRS (also the "key" secondary variable in 190-049).

Refer to Table VID3 for the definition of other secondary efficacy measures, including measures of subjective ratings or responses to questions via IVRS (completed each evening): daytime alertness, number of naps, nap time, daily ability to function, and sense of physical well-being. Table VID3 also shows definitions of subjective sleep measures, as well as evening questionnaire measures ("Next Day Effects" parameters) employed in Study 190-048 (as provided by the sponsor).

Statistical analysis was conducted on data from the ITT population (data of each efficacy variable was averaged over the double-blind treatment phase). The statistical test employed, to determine if significant treatment group effects could be revealed between the 2 mg ESZ group and the placebo group on each efficacy variable, was an ANOVA model with treatment and sites as fixed effects (with data rank-transformed).

Studies 190-047 and 190-048: Results on Disposition, Demographic Features, and Treatment Exposure

The disposition of subjects was previously described elsewhere in this review. Approximately 97% of subjects completed Study 190-047 and 91% of subjects completed Study 190-048. Treatment groups were generally similar on the incidence of subjects within each disposition category in both trials with the following exceptions. In Study 190-047 the incidence of placebo subjects who voluntarily withdrew from the study or who withdrew due to an adverse event were numerically greater (2.3% and 1.6%, respectively) than the incidence of subjects in the ESZ group (1.5% and 0.0%, respectively). Consequently, the placebo group had an overall incidence of 4.7% of subjects who discontinued from the study for any reason compared to only 2.2% of the 2 mg ESZ group.

Results on the disposition of subjects in Study 190-047 showed a higher incidence of subjects who voluntarily withdrew for any reason was in the 2 mg ESZ group (11.4%) compared to the placebo group (8.8%). The incidence in the 1 mg ESZ group was 6.9%. Surprisingly, a numerically greater percentage of placebo subjects withdrew from the study due to an adverse event (6.3%) compared to on 1.4% and 2.5% in the 1 mg and 2 mg ESZ groups, respectively. Another atypical finding was a somewhat large incidence of subjects who withdrew voluntarily in the 2 mg ESZ group (8.9%) compared to the low dose ESZ group and the placebo group (2.8% and 2.5%, respectively). An explanation for these atypical results cannot be found in the

study report (the corrected version of the study report, as provided in an amendment submission dated 3/25/03).

Treatment groups in each of the studies were similar on each demographic feature (the mean age, mean height and weight within each gender group, and in the distribution of subjects in gender and ethnic categories). The mean age of the subjects in each trial was approximately 72 years old and the majority of them were female (approximately 61 to 71% of subjects in each group of Study 190-047 and approximately 54 to 61% of subjects in Study 190-048). The demographic features of subjects in these trials were previously described in greater detail.

Treatment compliance of each treatment group in each of the trials was generally, approximately 99%. The mean exposure of the placebo group was 13.9 doses for 14.0 days and in the 2 mg ESZ group the mean exposure was 14.2 doses for 14.3 days. In Study 190-048 each treatment group had a mean of 13.1 to 13.3 doses of study drug for mean of 13.3 to 13.4 days.

Studies 190-047 and 190-048 Efficacy Results.

Since one trial was a PSG study and the other trial was a subjective sleep study (using IVRS), efficacy results are provided for each study, separately (as separate subsections below). Results on next-day and other sleep-related safety parameters from each trial follow, thereafter (in subsections after the efficacy result subsections). Refer to Section VIII for other safety information obtained from these trials.

Study 190-047 Efficacy Results.

Significantly shorter objective LPS and greater objective Sleep Efficiency was observed in the 2 mg ESZ group compared to the placebo group ($p < 0.0001$). These results were revealed when averaging data from both double-blind PSG visits (referred to as Nights 1 and 14, for each corresponding 2-night PSG visit).

Upon examination of Figure VID1 treatment group differences between the 2 mg ESZ group and the placebo group were numerically diminished over time and were no longer significant on Night 14 on the "key" parameter (objective WASO). Table VID4 in the appendix summarizes these results in tabular form (as provided by the sponsor).

The results on other secondary objective and subjective efficacy variables are summarized in Table VID5 and Figure VID2, respectively, in the appendix (as provided by the sponsor). These results were generally similar to those observed for the co-primary and "key" secondary variables. It is noted that the objective Wake Time After Sleep showed greater wake time in the ESZ group compared to the placebo group, which may be reflecting an earlier morning awakening observed in the ESZ group. Although, an explanation for these results cannot be found in the study report.

Figure VID2 shows objective cumulative wake time on Night 1, but results on Night 14 are not shown or described in the study report, where this information is described (section 11.4.1.4.1). Although, cumulatively wake time in the ESZ group appears to be less than that of the placebo group, the magnitude of the treatment group difference is primarily due to a shortened latency to sleep, as described by the sponsor in the study report (p. 60 of the 190-046.pdf file).

Results on Sleep Architecture

Table VI.D.5.I. summarizes results on sleep architecture. In summary these results generally showed small to absent treatment group differences on each parameter, in which some of these

differences reached a level of significance (without correcting for multiple comparisons). The greatest treatment group difference appeared to exist in non-REM stage 2, when examining differences on the actual median total sleep time in that sleep stage (in minutes). The ESZ group showed a longer sleep time spent in Stage 2 by 24 and 38 minutes longer than the placebo group on Nights 1 and 14, respectively. Treatment group differences on other parameters tended to be only a few minutes or no greater than 10 minutes in magnitude, as follows. A small increase in Stage 1 and small decreases in Stages 3/4 and REM (expressed as % of total sleep time and/or absolute time) in the ESZ group that were not observed in the placebo group.

"Next day" and "discontinuation" effects are discussed in a separate subsection that follows the next subsection on efficacy results in Study 190-048.

Study 190-048 Efficacy Results.

Results on the subjective primary efficacy variable (subjective sleep latency), the "key" secondary variable (subjective total sleep time), and on the secondary variable subjective WASO, generally showed trends for an effect that were similar to those observed in the objective PSG trial (Study 190-047). As in the PSG trial, treatment group differences showed a time-dependent decline, based on numerical comparisons between Weeks 1 and 2 (the greatest numerical treatment group difference on a given parameter appeared on Week 1 and generally became minimal to absent on Week 2). Neither the high dose nor low dose ESZ groups showed significant treatment group effects on Week 2 on the primary efficacy variable. These results are shown in Table VID6 and Figure VID3 (as provided by the sponsor).

The following describes important observations on primary and secondary variables, in more detail. Significant treatment group effects were not observed for the low dose ESZ group (1 mg group), and were not consistently revealed on all variables on all time-points (on Week 1 and 2) in the high dose ESZ group (2 mg group). Significant treatment group difference between the 2 mg ESZ group and placebo on the primary variable for the overall double-blind phase (averaging data from Weeks 1 and 2), appear to be primarily reflecting group differences found on Week 1 and not on Week 2. In Week 2, all three groups (placebo, 1 mg and 2 mg ESZ groups) were similar on median subjective LPS (see Figure VID3). Furthermore, the subjective results on each of the three parameters showed a similar time-dependent diminution or absence for significant treatment group effects on Week 2 compared to Week 1 (as shown the summary Figures in the appendix). These observations are similar to those revealed on objective PSG measures in Study 190-047.

A diminished effect over time may be reflecting a placebo effect between Week 1 and 2 of treatment. Based on numerical comparisons between Weeks 1 and 2 on results from the placebo group, the placebo group tended to show an improvement on a given parameter over time (between weeks 1 and 2), while the ESZ groups failed to show little to no change over time on median sleep latency and total sleep time. However, a potential placebo effect would not account for results on median WASO since a further decrease in this parameter occurred between Week 1 and 2 in all three treatment groups (placebo, 1 mg and 2 mg ESZ groups), as shown in Figure VID3. Furthermore, the median decrease in the 2 mg ESZ group over time (between Weeks 1 and 2) was numerically similar to (if not slightly greater than) the decrease in the placebo group.

A potential placebo effect also did not appear to explain a similar pattern for a diminished ESZ effect over time (between week 1 and 2 of double-blind treatment) in Study 190-047. In Study 190-047 the placebo group generally showed no change over time and in some cases showed a worsening over time (between Nights 1 and 14) on primary and secondary PSG variables, as shown in Figure VID1 in the appendix. Another difference between this PSG study and the subjective sleep study (Study 190-048) is that the PSG study only had a 2 mg ESZ group, while Study 190-048 included a 1 mg ESZ group. This lower dose group was not significantly different from placebo on all three subjective sleep parameters (but showed small trends for an effect) except for on week 1 on the primary variable (median subjective sleep latency) in which effects were significant. This observation would suggest a dose-dependent effect on the diminution of an ESZ effect over time (that is a possible dose-level by time interaction effect on efficacy).

The secondary variable (subjective number of awakenings) failed to show any significant treatment group differences between either the 1 mg or 2 mg ESZ groups and placebo for the overall double-blind treatment phase, or for each week (Weeks 1 and 2) in Study 190-048.

Results on Next Day Effects and Rebound Effects (Studies 190-047 and 190-048). Next-day effects were examined in Studies 190-047 and 190-048. Rebound effects were only examined in Study 190-048. Results of Study 190-047 are first described below, followed by results of Study 190-048.

Next Day Effects in Study 190-047. As shown in Table VID7A in the appendix (B shows results of 190-048 for comparison), treatment groups were generally similar on subjective "next-day effects" parameters (data collected in the mornings via IVRS): daytime alertness, total nap time, daily ability to function, and sense of well-being. The sponsor describes results on morning sleepiness (data from morning IVRS assessments) and on the number of naps, as showing significant treatment group effects in favor of ESZ treatment over placebo. However, these comparisons were not corrected for multiple comparisons, and they only showed a level of significance of the either $p \leq 0.1$ or ≤ 0.05. Furthermore, treatment group differences were very small, if not clinically insignificant. Any small differences that were observed occurred primarily at Week 1, and not at Week 2. Therefore, in the opinion of this reviewer, there were no treatment group effects on any of these "Next Day Effect" parameters. Similar results were revealed for Insomnia Severity Index parameters (as shown in Table 11.4.1.4.5-1 on p.65 in the 190-047.pdf file).

Study 190-047 Results on Rebound Effects.

Results on Rebound Effects on Efficacy Parameters. As shown in Figures VID4 in the appendix treatment group differences on each subjective sleep parameter (median sleep latency, median total sleep time and median WASO) on treatment discontinuation nights (Nights 15 and 16) appeared to exist on Night 15 on each parameter, and on both nights on the median WASO. Some of these differences reached a level of significance as shown in the summary tables (figures were provided in the study report of the original submission but were modified by this reviewer to include all efficacy time-points for comparison). When numerically comparing these results to results on Nights 14 during the double-blind phase of the placebo, the ESZ groups showed a fairly marked change between Night 14 (at the end of the 2-week double-blind

treatment phase) and Night 15 (the first night after cessation of double-blind treatment) on each of these parameters. As anticipated this change was a worsening on a given efficacy parameter over time between these two time-points. While these results suggest a lack of efficacy associated with cessation of treatment, the placebo group showed a marked improvement between Night 14 (the end of treatment) and Night 15 (the first night after treatment cessation), suggesting that observations in the ESZ group could be reflecting rebound effects (instead of a lack of efficacy). Furthermore, the treatment groups merged (were similar) on median values of two of the three parameters on the second rebound night (median sleep latency and total sleep time, but not on median WASO). It is also important to note that on median WASO failed to reveal a significant treatment group effect between ESZ and placebo on Night 14 of the double-blind treatment phase (but trends for an effect did appear to exist). Consequently, the results show that while the ESZ group showed a worsening, the placebo group showed an improvement upon treatment cessation on each of these parameters based on numerical comparisons of the data. While the ESZ group showed values on Night 15, similar to those at baseline, one cannot assume that this is evidence for the absence of rebound effects due to observed differences in the placebo group. Furthermore, other confounding variables and limitations in the study design must also be considered when making such a conclusion (e.g. subjects did not receive single-blind placebo during the rebound nights).

Because of the observations on both placebo and ESZ groups, discontinuation effects must be considered, particularly since the most prominent treatment group differences occurred on the first, rather than on the second night after treatment cessation on at least two of the three parameters. It is noted that neither groups received a single-blind placebo treatment during these two discontinuation nights. Other potentially confounding variables were not controlled for in this trial. Therefore this trial has a number of limitations in the interpretation of the results.

It is not clear why the study report does not describe any results on sleep efficiency on the discontinuation nights (in text section 11.4.1.4.6 on this topic), since sleep efficiency was a co-primary variable.

Results from an insomnia scale (Insomnia Severity Index) are shown for Day 14 and End-of-Study Visits and failed to reveal any remarkable findings.

Results of Rebound Effects on Sleep Architecture. Results of potential rebound effects on sleep architecture could not be found in the study report.

Results of Rebound Effects on AE's (Withdrawal AE's).

Table VID8 in the appendix shows the incidence of withdrawal AEs reported between 24-72 hours after the last double-blind dose. Withdrawal AEs were reported in 16.2% in the ESZ group compared to only 10.9% in the placebo group. The following Body System AEs had an incidence that was numerically greater in the ESZ group compared to placebo (the incidence in the placebo and the 2 mg ESZ groups is shown):

- Body as a whole (5.5%, 9.6%): accidental injury (0%, 3%), back pain (0%, 2.2%), pain (0.8%, 2.9%)
- Digestive System (0.8%, 1.5%)
- Musculoskeletal System (0%, 1.5%)
- Nervous System (0.8%, 3.7%): abnormal dreams, anxiety, dizziness, insomnia, nervousness, and somnolence each occurred in one ESZ subject and in no placebo subjects.

Study 190-048 Results on Next Day Effects (Rebound Effects Were Not Examined in this Study).
Table VID7B shows the results on morning subjective IVRS ratings (each rating was on a scale from 0 to 10, with 10 representing the best outcome and 0 representing the worst outcome). Only very small trends for a higher scores in only the high dose ESZ group (the 2 mg group and not in the 1 mg group) compared to placebo were revealed. None of the pairwise comparisons revealed p values beyond a p of <0.05 (without correcting for multiple comparisons) and the treatment group differences were less than one unit on each 10 point scale. Nap time, expressed in minutes, only revealed trends for shorter nap time in each ESZ group than nap time in the placebo group. There are treatment group difference was only approximately seven minutes. In the opinion of this reviewer, these results do not support a significant treatment group effects on "next day effects" for greater improvement with ESZ treatment, but rather show that ESZ is similar to placebo on these parameters.

Withdrawal AE's. A description of withdrawal AE's cannot be found for Study 190-048. Perhaps, withdrawal AE's were not examined in this trial since the last study visit occurred on Day 15 to 17 (the end of the double-blind treatment phase). However, it is not clear why the subjects were not followed for withdrawal AE's over a few days after Day trial with treatment cessation.

Studies 190-047 and 190-048: Results on the Incidence of Unpleasant Taste.
Since unpleasant taste may compromise the double-blind to the study drug, the incidence of this AE in subjects of each study is shown below:

- **Study 190-047:** 0 and 13%, in placebo and the 2 mg ESZ groups, respectively.
- **Study 190-048:** 1.3% (1/80 subjects), 8.3% and 11.4%, in placebo, 1 mg and 2 mg ESZ groups, respectively.

As in previous trials, these results show a drug-related and dose-related effect on the incidence of unpleasant taste. Given these observations, the double-blind study design was compromised, whereby impacting on the interpretability of efficacy, next-day and discontinuation results (e.g. that subjects and investigators/research staff believed that an unpleasant taste was due to ESZ, such that subjects having bad taste were assigned to ESZ).

Studies 190-047 and 190-048: Conclusions
These studies, showed at least trends for an effect of 2 mg ESZ over placebo on subjective or objective sleep parameters, but the effects diminished over 2 weeks or became absent by treatment endpoint (between Weeks 1 and 2 of treatment). Results on the two rebound nights suggest a potential rebound effects of the study drug in both trials, as previously described. In study 190-047 the value of efficacy parameters in the ESZ. groups were numerically greater than values at baseline, which is evidence that further supports the potential for a rebound effects with the study drug.

In the opinion of this reviewer the interpretability of the results of both trials is seriously compromised, as in other trials, due to unpleasant taste associated with the study drug. Unpleasant taste was a common AE showing a dose-dependent pattern in ESZ subjects (the incidence in 2 mg ESZ subjects was numerically greater than the incidence in the 1 mg ESZ group in both trials). This observation is reproducible (as described for other trials in this

review), occurs in single-dose trials (see Study 190-026, below), as well as multiple-dose trials, and in some studies the incidence of ESZ subjects with this AE is over 20 to 30% at the proposed recommended dose-level of 3 mg for non-elderly patients. The impact of unpleasant taste associated with the study drug, which is commonly reported among ESZ subjects (with no to only few placebo subjects with this AE) is a serious concern regarding the integrity of the double-blind study design, and in turn the interpretability of study results.

E. Healthy Non-Elderly Adults in a Study 190-026 Using a Transient Insomnia Model
Study 190-026: Objectives
The primary objective of this study was to examine "hypnotic efficacy, safety and tolerability" of a single dose of ESZ treatment (an oral solution formulation) compared to placebo in healthy adults using a first night effect model for transient insomnia.

Study 190-026: Study Design and Subjects
This multicenter, double-blind, placebo-controlled trial employed a parallel group design in which 436 generally healthy 25 to 50-year-old male and female subjects were randomized (using a 2:1:2:2:2 ratio) to receive a single dose (30 minutes before the subject's average bedtime) of one of the four following treatments (using an oral solution of active drug will and placebo):

- Placebo, 25 ml (the vehicle: a sodium phosphate buffer)
- 1.0 mg/25 ml ESZ will
- 2.0 mg/25 ml ESZ
- 3.0 mg/25 ml ESZ
- 3.5 mg/25 ml ESZ

Screening occurred within 14 days of dosing. Eligibility criteria were similar to those in Phase I trials in that the subjects were 25 to 50 years old, generally healthy, and did not have any clinically significant abnormal findings on clinical assessments at screening. Subjects could not have symptoms consistent with a sleep disorder (and could not have regular shifts in their sleep schedule). PSG screening was not employed to rule out sleep apnea, periodic leg movements syndrome or other sleep disturbances (the study used a first-night-effect, transient-insomnia model). Any previous experience in a sleep laboratory, or previous exposure to ESZ treatment are additional key exclusionary criteria. To be eligible in the study subjects had to report a sleep pattern that met the following criteria:

- A usual bedtime between 21:00 and 24:00 hours.
- Sleep onset < 30 minutes.
- Sleep duration = 6.5 to 10.0 hours/night.
- Does not report, a decrease in daytime function due to sleep disturbances.
- Lights-out Time between 21:00-24:00 hours (based on results from five consecutive Morning Questionnaires obtained prior to the dosing visit).

Women of childbearing potential had to practice an acceptable contraceptive method (could use oral contraceptive agents but must be on a stable dose). Subjects were screened for Hepatitis B and C.

Table VIE1 in the appendix shows the schedule of assessments during the study (as provided by the sponsor). Subjects were to arrive at a sleep laboratory at 2.5 hours prior to their mean time of lights-out (bedtime) which was time-point determined from bedtime data from five consecutive

Morning Questionnaires completed prior to the study. Subjects were instructed to have dinner prior to arrival.

Pre-dose assessments (including vital sign measures, DSST, and others) were obtained in the evening prior to dosing. Subjects received their assigned, double-blind treatment at 30 minutes prior to lights out (lights out were scheduled to occur at ±15 minutes of the mean lights-out time, calculated from Morning Questionnaires, as previously described). Subjects underwent PSG recording. PSG recording occurred over a period of 8 hours, upon which subjects were awakened if necessary. After morning awakening subjects underwent post-dose assessments as shown in Table VIE1. This included completion of the Morning Questionnaire and the administration of the DSST.

Study 190-026: Efficacy Assessments

The definitions of objective sleep measures (including sleep architecture measures), subjective sleep measures from that Morning Questionnaire were generally similar to those of previously described trials.

Study 190-026: Statistical Analysis of Primary and Key Secondary Variables

The primary efficacy variable was Latency to Persisting Sleep (LPS). The primary analysis was conducted on the ITT population using statistical methods similar to those employed in previous trials. As in previous trials, an ANOVA model was employed with treatment and site as fixed effects on rank-transformed data. The primary analysis was conducted on data from the two high dose ESZ groups (3.0 and 3.5 mg groups) and placebo group. If a significant treatment group effect was revealed ($p < 0.05$), then pairwise comparisons between each of the higher dose ESZ groups (3.0 and 3.5 mg ESZ groups) and the placebo group was conducted using the ANOVA model.

According to the study report objective sleep efficiency was a key secondary variable, but instead of analyzing data from the ITT population, data was analyzed from an "evaluable" population, as defined later. It is also not clear in the statistical analysis section of the study report (9.7 in the 190-026.pdf file) which treatment groups were included in the statistical analysis of data on the "key" secondary variable (i.e. if only the 3 and 3.5 mg ESZ groups and the placebo group, were included for the primary variable). A secondary analysis on the primary and other non-key secondary variables was conducted using the Evaluable population data set.

The rationale for using one dataset for the primary analysis on the primary variable (as well as on non-key secondary variables) and using another dataset for analyzing data on the "key" secondary variable cannot be found in the study report (ITT population was the data set used for the primary and all other secondary variables).

The "Evaluable" population (from which data was used for the primary analysis of the "key" secondary variable) is defined elsewhere (not in the section on the primary statistical analysis) in the study report as follows: *this population was identified by Evaluability Committee based on blinded review of protocol deviations prior to unblinding.*

The above definition does not clarify which subjects of the ITT population were excluded from the "Evaluable" population and why these subjects were excluded (i.e. selected over other subjects that deviated from the protocol). However, Section 11.1 in this study report indicates that two subjects who were randomized twice to double-blind treatment (it appears these two subjects participated in the study on two occasions at two different study sites), who were included in the ITT population but were not included in the "Evaluable" population. The

following observations regarding this population are noted, based on an examination of the end-of-text summary tables of the study report (Tables 14.1.1 and 14.1.2). The number of evaluable subjects in each treatment group (as provided in the disposition summary table) matches the number of subjects in each treatment group that was identified as having an "important" protocol deviation. The categories of protocol deviations shown in Table 14.1.2 were the following: has a usual sleep latency > 30 minutes or usual sleep time < six hours, deviated dosing time by at least 15 minutes relative to lights-out time, a PSG recording time of ≤7.5 hours, subjects dosed with "zopiclone" stock solution < 80%, subjects who violated sleep pattern criteria on the night before dosing, subjects participating more than once in the study. Based on these observations it appears that the "evaluable" population was the ITT population excluding subjects identified by a committee as having an "Important" Protocol deviation.

Based on the results shown in the End-of-Test Summary table (Table 14.1.2) it is noteworthy that 9% to 16% of subjects in any given treatment group had an "important" protocol deviation. It is particularly remarkable that 4% to 6% of subjects in any given treatment group were dosed with "Zopiclone stock solution <80%" (refer to Table 14.1.2 on p. 74 of the Study report pdf file). It appears that "zopiclone" listed in the summary table was actually ESZ, since the text section of the study report (Section 10.2 on p. 42 in the 190-026.pdf file) refers to the stock solution as the "(S)-zopiclone stock solution <80%". In Section 9.4.2 of the study report (on p. 22 of the PDF file), the stock solution had a 0.5 mg/ml concentration of ESZ. However, further clarification is needed to verify this information, as well as the actual dose that was received by the subjects. Further clarification is also needed regarding the selection of subjects who were excluded from the "Evaluable" population and why the primary analysis was not consistently conducted on the same dataset for both primary and key secondary variables.

Study 190-026: Results on Disposition, Demographic and Treatment Exposure

All subjects completed the trial except for one placebo subject left prematurely due to a family emergency. Therefore, all the remainder subjects received a single dose of double-blind treatment. Yet, given the results on protocol deviations that included up to 6% of subjects receiving an active drug stock solution in a given treatment group, it is not clear which subjects in which treatment group received what drug (placebo versus ESZ and at what dose).

Common types of "important" protocol deviations (showing an incidence of >3% in any given group) were the following (the incidence of placebo, 1 mg, 2 mg, 3 mg and 3.5 mg ESZ groups as provided):

- An "important" protocol deviation of any type (14%, 15%, 14%, 16%, 9%, respectively).
- A usual sleep latency > 30 minutes or sleep time < six hours (2%, 6%, 5%, to percent, 0%).
- Dosing time deviated > 15 minutes relative to lights-out time (2%, 0%, 3%, 4%, 1%).
- Dosed with "zopiclone" stock solution <80% (6%, 4%, 5%, 4%, 4%).
- Violated sleep pattern criteria on the night before dosing (3%, to percent, 0%, 4%, 3%).

As previously mentioned some subjects received a stock "zopiclone" solution instead of their assigned study drug. Another protocol deviation worth noting is regarding subjects who participated in the study twice, of which their data was included in the ITT population (as four subjects), as previously described.

See Table VIB4 in the appendix for demographic features of the subjects. Treatment groups were generally similar on each demographic feature (in mean age, and mean height, weight and BMI in each gender subgroup and in the distribution of subjects in each gender and ethnic subgroup). Unlike trials on patients with chronic insomnia, subjects were younger and consisted of fairly equal numbers of men and women in each group.

Study 190-026: Efficacy Results
Given, serious problems with the interpretability of the data efficacy results are not described as they cannot provide clinically meaningful results as presented by the sponsor, in the opinion of this reviewer. The serious problems have been previously described, and are also outlined in the conclusion section on this trial below.

Study 190-026: Results on DSST. Based on visual examination of the results summarized in Table 12.6-1 in this study report (p.65 in the 190-026.pdf file), a drug-related impairment on DSST of the ESZ treatment was revealed, as described in the following. The greatest mean improvement in performance (mean change in the DSST score) from pre-dose (60 minutes before dosing) to post-dose (10 hours after treatment) was observed in the placebo group (6.4±7.7 units or 13% improvement). Each ESZ group generally showed less improvement (the 1 mg, 3 mg and 3.5 mg groups, mean change of 2.5±11.6, 5.8±12.6, 1.3±11, respectively or 4-7% percent change among the groups), except for the 2 mg ESZ group. The 2 mg ESZ group had a similar mean change to that of the placebo group. The least improvement was observed in the 3 mg ESZ group (mean change of 1.3±11 or 4% improvement). Treatment group differences between each ESZ group and the placebo group reached a level of significance of $p < 0.02$-0.0001, with the exception of the 2 mg ESZ group ($p = 0.63$).

Study 190-026: Conclusions
The following presents a serious problem in the ability to interpret the results of this study. A subgroup of subjects received a stock solution of an active drug (the active drug received was either zopiclone or ESZ as an 80% stock solution), instead of their assigned study drug. The incidence of subjects receiving this stock solution ranged from 4% to 6% in any given group. The sponsor analyzes data collected from these subjects for the primary analysis of the primary variable, while it appears that the data used for the analysis on the "key secondary" variable excluded these subjects along with subjects who had other types of "important" protocol deviations. It is also not clear why some protocol deviations were considered "important" and why these were used in selecting subjects for the primary analysis of the "key" secondary variable. It is also not clear why different a dataset was used for the primary analysis (and for other non-key secondary variables) than on the primary efficacy variable than the dataset used for the analysis of the "key" secondary variable. Therefore, the results as presented are not, in the opinion of this reviewer, interpretable. Perhaps, consideration may be given to conducting an analysis of the ITT population that only excludes data from the subjects who received a stock solution of active drug, rather than their assigned study drug.

Another serious problem with the ability to interpret the study results is that approximately 20% of subjects in each ESZ group reported unpleasant taste. Not surprisingly, 7.1% of placebo subjects reported unpleasant taste, given that 6.1% of placebo subjects received a stock solution of active drug (either zopiclone or ESZ) instead of placebo.

Another potential problem in the interpretation of the study results of Study 190-026 is that an oral solution formulation was used, instead of the tablet formulation that is proposed in labeling. However, based on a 7/31/03, e-mail communication with Dr. Jackson, OCPB Reviewer, the oral solution used in Study 190-026 is acceptable from a pharmacokinetic perspective whereby efficacy and safety results of the trial can be extrapolated to being applicable to the marketed tablet formulation (i.e. absorption of the oral solution is comparable to that of the tablet formulation).

Finally, DSST results in Study 190-026 show less improvement on performance in ESZ groups compared to placebo.

F. Results of Subgroup Analyses of Efficacy Data in Demographic Subgroups.
These results were described for most individual studies on selected demographic features (e.g. depending on the distribution of subjects within a give demographic subgroup and sample size). Integrated subgroup analyses were not conducted (data from multiple trials were not pooled). Individual study analyses generally failed to reveal any remarkable findings and generally showed trends for efficacy in a given subgroup, with some exceptions previously noted in this review. However, the trials were designed to specifically examine effects of ethnicity, gender and age on efficacy, and subgroup sample sizes were often insufficient, such that most of the results on subgroup analyses are considered preliminary or exploratory in nature.

G. Overall Conclusions.
Efficacy results of the Phase III trials generally revealed highly significant treatment group effects in favor of ESZ treatment in Chronic Insomnia patients over placebo at the proposed dose levels (3 mg bedtime dose for non-elderly patients and a 2 mg bedtime dose for elderly patients) on primary and key secondary PSG and sleep diary measures. However, several problems were observed regarding the interpretability of the efficacy results from all or most of these trials, as follows:

- Unpleasant taste was associated with the study drug when given as either single or multiple doses and was reported in up to approximately one-third of 3mg ESZ the treated subjects in a given Phase III trial, while the incidence of unpleasant taste in placebo subjects was generally ranged from <1% to 3% among the trials. The incidence of unpleasant taste was dose-dependent in trials using multiple dose levels of ESZ. Therefore, the placebo was not adequately matched to the ESZ study drug, such that the integrity of the double-blind design of the study was likely to have been seriously compromised. Consequently, the interpretability of efficacy and other results of these trials is of grave concern that in the opinion of this reviewer, needs to be addressed, as further described in Section XI on Conclusions and Recommendations in this review.
- A subgroup of subjects were selected in at least some of the trials as "evaluable" subjects from which the data was used for the primary efficacy analyses, but not used for other efficacy analyses (as described for Study 190-026). A committee identified subjects who had "important" protocol deviations from which their data was not considered "evaluable." See Section VC, above, for further details, as well as sections below. It is not clear if these methods for selecting "evaluable" subjects were used for selecting a subgroup data for conducting primary versus secondary analyses was used in other Phase III trials. If indeed this method was employed as described in this review then the interpretability of the efficacy results is in the opinion of this reviewer compromised.

Rebound, Tolerance and Next-day effects were previously discussed, but in summary generally showed these effects on the basis of that previously described.

Refer to Section XI of this reviewer for additional concerns with these studies and for overall conclusions and recommendations.

VII. Studies on Specific Safety Assessments Relevant to the Drug-Class: Studies 190-024 and 190-025 on "Next-Day" Effects, Study 190-012 on Respiratory Drive Effects, and Study 190-015 on Alcohol Interaction Effects.

Studies 190-024 and 190-025 were studies on next-day performance effects of ESZ on psychometric measures in healthy volunteers. Next-day effects were also conducted in several efficacy trials, as previously described. However, since Studies 190-024 and 190-025 were not efficacy trials and were among trials focusing on specific drug-class safety issues, these trials are described in this section of the review.

Studies 190-012 and 190-015 are also studies focusing on specific drug-class safety concerns and are also described in this section. The former trial examined ESZ effects on respiratory drive parameters, while the latter study examined potential ESZ-alcohol interaction effects on psychometric parameters.

A. Next Day Performance Trials (Studies 190-024 and 190-025)

Objectives

Studies 190-024 and 190-025 were four-way crossover studies examining the effects of a single dose of ESZ (2 mg or 3 mg) to placebo on next-day performance on a battery of neuropsychological tests. Both studies included a single-dose treatment condition of 30 mg flurazepam, as an active comparator.

These studies were virtually identical except that study 190-024 was conducted on generally healthy male and female subjects, while study 190-025 was conducted on patients with Chronic Insomnia (by DSM-IV criteria).

Study Design and Subjects in Studies 190-024 and 190-025.

Study Design. Both studies employed a single-center, double-blind, randomized, placebo-controlled, four-way crossover design in which subjects were randomized to a treatment sequence of four treatment conditions, as follows:

- **Treatment condition A:** placebo (2 placebo tablets and 1 placebo capsule).
- **Treatment condition B:** 2 mg ESZ (2 tablets of 1.0 mg ESZ/tablet and 1 placebo capsule).
- **Treatment condition C:** 3 mg ESZ (2 tablets of 1.5 mg ESZ/tablet and one placebo capsule).
- **Treatment condition D:** 30 mg flurazepam (1 capsule of 30 mg/capsule and 2 placebo tablets).

Subjects were randomized to one of the following treatment sequences (in a 1:1:1:1 ratio):

- Sequence I: ABDC
- Sequence II: BCAD
- Sequence III: CDBA

- Sequence IV: DACB

Subjects received a single dose of assigned study drug on the first night of Visits 2 through 5 of the study (each of these visits was over two days). The methods for each study visit is summarized in the following and also shown in Table VIIA1, in the appendix (as provided by the sponsor):

- **Visit 1.** Subjects underwent screening, training sessions on Cognitive Drug Research (CDR) computerized assessments (practice sessions could also occur on Day 1 of Visit 2, described below).
- **Visits 2-5.** Eligible subjects returned to the clinic, 20 days after Visit 1. On Visit 2 subjects were randomized to their assigned treatment sequence. Visits 2 through 5 were each 2 days long and visit was separated by a wash-out period of 14±2 days. Subjects were fed standardized meals during their visits.

  On Day 1 of each visit subjects were given dinner at no later than 18:00. CDR assessments were conducted at 60 minutes prior to administration of the assigned study drug. Study drug was given (as a single oral dose) on the first evening of each visit (at 22:00). Subjects were required to go to bed with the lights out at 30 minutes postdose.

  On Day 2 subjects were awakened in the morning at 8.5 hours postdose and were given breakfast. CDR assessments were re-administered at two time-points on Day 2: at 9.5 hours and 12.5 hours postdose. CDR assessments are described in more detail below.

A list of the CDR computerized assessments and a description of each of the tests is provided in Tables VIIA2-4 of the appendix. Table VIIA2 lists the tests in the order that they were administered. Parallel forms of the tests were used for each testing session. The following information could not be found in the study reports: the duration of each testing session, references and a description of the reliability and validity of these tests. Also, a description on methodology for controlling for potential practice and test-order effects could not be found in the study report.

Subjects underwent additional safety assessments as shown in the Schedule of Assessments in Table VIIA1. Vital sign measures do not include orthostatic measures. Pharmacokinetic measures were not obtained in these studies.

Subjects. The subjects of both studies were male and female generally healthy subjects between the ages of 21 to 64 years old. Screening assessments and other eligibility criteria were generally similar to those employed in other trials.

Subjects in study 190-025 were required to meet DSM-IV criteria for Chronic insomnia, as well as, meeting the following criteria on reported sleep patterns for a period of at least one month prior to study entry:

- No more than 6.5 hours of sleep each night.
- Sleep latency > 30 minutes each night.

The patients in Study 190-025 could not have other types of sleep disturbances (e.g. sleep apnea, restless legs syndrome, periodic limb movements, and could not be rotating or third-shift workers).

Subjects in Study 190-024 were required to have no sleep disturbances as in the following:

- Could not have a reported average sleep duration < 9 hours/night.
- Could not have difficulty in sleep initiation or maintenance associated with a known sleep disorder.

- Could not be a rotating or third-shift worker.

Studies 190-024 and 190-025: Next Day Performance Assessments
Primary and secondary "Next-Day Performance" variables consisted of composite measures using data collected from the CDR assessments. These composite scores are described in Table VIIA4 in the appendix (as provided by the sponsor). As previously mentioned, Table VIIA2 lists the CDR assessments and Table VIIA3 describes each assessment.

As described in Table VIIA4 the "Quality of Working Memory" composite measure (a secondary variable) was calculated using "Sensitivity Indices." These indices are defined on page 22 in the study report (and that 190-024.pdf file). A nonparametric sensitivity index is based on a calculation using a formula by Frey and Colliver (date could not be found for a specific reference in the section of the study report describing this index measure). Accuracy scores to original and novel (destructor) information on tests of working memory and recognition tasks were summated before calculating the index score using the Frey and Colliver formula. The sensitivity index was intended to reflect both, the ability to identify previously presented items, as well as correctly rejected items that were not previously presented to the subject. The sensitivity index score ranged from zero to one. A score of zero was intended to represent chance performance (no sensitivity to the task information) and the maximum score of one was intended to represent perfect recognition performance.

Primary and Key Secondary Variables on Next-Day Performance
Primary Variable:

- Power of Attention was the primary variable and is defined as the sum of each of the following scores: Simple Reaction Time, Choice Reaction Time, and Digit of Vigilant Detection Speed scores.

Secondary Variables.
Secondary variables were the following composite measures: Speed of Memory Index, Quality of Working Memory, Quality of Secondary Memory, and Continuity of Attention. Refer to Table VIIA4 for a description of each composite measure. Digit Symbol Substitution Test (DSST) score was also a "next-day" secondary measure.

Statistical Analysis Methods on Next-Day Performance Variables.
An ANCOVA was employed to determine treatment, sequence and period effects on the change from baseline to 9.5 hours postdose on primary and secondary composite measures, with the baseline score as a covariate. This analysis was conducted with subjects nested within sequence as a random effect. Secondary analyses were also conducted on the mean change from baseline to 12.5 hours postdose on the primary and secondary measures. These analyses were conducted using data from the ITT population (randomized subjects who had at least one dose of study drug).

Studies 190-024 and 190-025: Disposition in Demographic Features of the Subjects.
Demographic features of subjects in Studies 190-024 and 190-025 are summarized in Table VIIA6 in the appendix (as provided by the sponsor). Differences in demographic features between subjects in Study 190-024 and subjects in Study 190-025 are described in the following and are generally consistent with differences in the eligibility criteria employed in these two

studies (Study 190-024 was conducted on generally healthy adults and Study 190-025 was conducted on patients with Chronic Insomnia). Subjects in Study 190-024 had a mean age 39 years old (ranging from 28 to 53 years old) compared to a mean age of 46 years (ranging from 28 to 64 years old) in subjects of Study 190-025. There were equal numbers of men and women in Study 190-024, while in Study 190-025, approximately 70% of the subjects were women. All of the subjects in Study 190-025 were Caucasian, while 75% of subjects were Caucasian and 25% were "Black" in Study 190-025.

All 12 subjects in each of the two trials completed the study. However, one subject described in Section 10.2 of the study report of Study 190-025, voluntarily withdrew early after only receiving one dose of placebo. But later, this subject reentered in the study and completed the protocol. After initiating the study, the protocol was revised due to concerns "over the adequacy of the drug blinding procedures for the active comparator." This revision occurred after randomizing and treating four subjects (as described in section 9.8.1 in the study report). One of these four subjects, reentered the study and is the same subject as the above-described as subject who voluntarily withdrew early, but then returned and completed the trial. A description of the protocol revisions to improve drug blinding procedures cannot be found (the revision is only mentioned, yet it is not described, in section 9.8.1).

Studies 190-024 and 190-025: Results on Next-day Performance Measures
Results on primary and secondary variables are shown in Tables VIIA7-8 for Study 190-024 and in Tables VIIA10-11 for Study 190-025 in the appendix (as provided by the sponsor). Results on the statistical analysis for an overall treatment effect using an ANCOVA (as described in the statistical methods section of the study reports), cannot be found in the study report. Instead, only the results of pairwise comparisons between each active treatment condition to the placebo treatment condition on each variable are shown in the sponsor's summary tables. The results in the summary tables generally show no significant treatment group differences with a few exceptions. In the few exceptions a significant ($p<0.05$) worsening on performance was observed in either the 3 mg ESZ treatment or the 30 mg flurazepam treatment compared to placebo at 9.5 hours or 12.5 hours postdose.

It is important to note that while significant treatment group differences were not revealed on many parameters at either of the two postdose time-points, several parameters did show trends for a treatment effect and in some cases the trends were dose-dependent between the low and high dose ESZ treatment conditions. Furthermore, some of these trends for an effect were large in magnitude with large treatment group differences. Perhaps, failure of these large group differences to reach a level of significance was due to a large variance observed on these measures.

The exceptions to failing to reveal significant treatment group differences on a given parameter are described for each study in subsections below.

Study 190-024 on Healthy Subjects and Study Results. One exception, in which a significant treatment group effect was revealed in Study 190-024 was on the primary variable, Power of Attention (in milliseconds). The 3 mg ESZ treatment showed significantly worsening from baseline to 9.5 hours postdose on this parameter compared to placebo (LS means of 51.0 and 5.2

msecs in 3 mg ESZ and placebo treatment conditions, respectively). This treatment effect was no longer observed at 12.5 hours postdose as shown in Table VIIA7.

The 2 mg ESZ treatment condition also failed to show significant treatment effects on each variable, except for Speed of Memory in Study 190-024 in which there were significant worsening at 9.5 hours postdose, but only trends for worsening at 12.5 hours postdose compared to placebo. The 3 mg ESZ group showed similar significant effects on this parameter in Study 190-024.

Study 190-025 on Patients with Chronic Insomnia and Study Results. A significant treatment group effect on the primary variable, previously observed in healthy subjects in Study 190-024, could not be reproduced in Study 190-025 on patients Chronic Insomnia. Furthermore, results for treatment group effects on Speed of Memory observed in Study 190-024 were also not reproducible in Study 190-025. Instead, the Chronic Insomnia patients showed significant worsening on Quality of Secondary Memory from baseline to 12.5 hours postdose, but not at 9.5 hours postdose in the 3 mg ESZ treatment condition compared to placebo. No other parameters showed significant treatment group effects between either the high or low dose ESZ treatment conditions compared to placebo.

Results on flurazepam in Studies 190-024 and -025 are noted in this paragraph, as this treatment condition can be potentially viewed as an internal standard or control in each study. The flurazepam treatment condition showed significant worsening on a few of the parameters and time-points as follows (based on the previously mentioned summary tables in the appendix):

- Study 190-024 - Power of Attention at 9.5 hours, Speed of Memory at 9.5 and 12.5 hours.
- Study 190-025 - None of the variables at any time point, except for trends for a worsening on the following variables: Quality of Secondary Memory at 9.5 hours ($p<0.08$), Speed of Memory at 12.5 hours ($p < 0.068$).

It is important to realize that the above results need to be interpreted with caution, given the possibility for a Type II error due to multiple comparisons. Yet, the above variables showing significant effects, or trends for an effect, are the same variables that showed significant effects of ESZ treatment compared to placebo in each respective trial.

Parameters that failed to show significant effects for either ESZ or Flurazepam in Studies 190-024 and -025. An absence of significant treatment group effects for any of the pair-wise comparisons between each active treatment condition to placebo could be reflecting the absence of assay sensitivity in that given study. Therefore, this paragraph describes parameters that failed to show any treatment group effects for any of the time points. The following parameters failed to show any significant treatment group effects at any of the time points (refer to previously mentioned summary tables in the appendix for further details):

- Study 190-024 - Quality of Working Memory, Quality of Secondary Memory, Continuity of Attention.
- Study 190-025 - The primary variable; Power of Attention, Quality of Working Memory, Continuity of Attention.

Since, Quality of Working Memory only has a range values from 0 to 1, it would appear that an absence of significant treatment group effects could be due to floor effects on this parameter. While, other parameters listed above, failed to show treatment group differences that reached a

level of significance (i.e. $p < 0.05$), some of these parameters did showed trends for a worsening effect of ESZ compared to placebo and/or flurazepam treatment compared to placebo as shown in the summary tables in the appendix. Furthermore, none of the parameters appeared to show any trends or values in the direction of improvement from baseline to each postdose time point in the 3 mg ESZ and flurazepam treatment conditions. Nevertheless, only a few variables showed mean changes in the direction for improvement in the placebo treatment condition, as well.

Results on DSST in Studies 190-024 and 190-025. Results on DSST performance are shown in Tables VIIA9 and VIIA12 and were generally similar to the results on other Next-Day parameters. No significant treatment group differences were revealed on the mean change from baseline to each post-dose time-point (at 9.5 hours and 12.5 hours post-dose).

Studies 190-024 and 190-025 Next Day Performance Trials: Conclusions
Trends and in some cases significant effects of ESZ compared to placebo on worsening of test performance was observed on some of the variables in the two studies. Upon visual inspection of the summary tables of results on each variable, trends for large group differences on test performance were observed in the trial on healthy subjects on a number of parameters (in the direction of worsening from baseline to post-dose with ESZ treatment compared to placebo). Similar trends were observed in the trial on patients with Chronic Insomnia, except the numerical group differences were smaller. These studies had several limitations, such that the results are not considered by this reviewer as clear evidence for the absence of next-day effects. These limitations are outlined below.

The following are some problems with the study design of both studies or are issues that did not appear to be addressed (a discussion or description of methodology employed to minimize these potential issues or confounding variables):

- Potential practice, test-order and time-of-day effects on test performance. Regarding the concern of potential time-of-day effects on test measures note that baseline values were obtained on the night before, and next-day values were obtained in the morning and 12.5 hours postdose with correspondent with afternoon-time.
- References and a discussion on the reliability and validity of each cognitive or neuropsychological test could not be found in the study reports.
- Similarly, references and a discussion on the reliability and validity of composite scores could not be found in the study reports.
- Some parameters showed fairly consistent and large values for a mean decline in performance compared to placebo, yet did not reach a level of significance. Yet, variance was large, suggesting that potential confounding variables were not adequately controlled for in the studies. Another consideration on at least some parameters is the potential for floor effects. The lack of adequate assay sensitivity should also be considered, since flurazepam treatment failed to show significant effects compared to placebo on many of the parameters, including the primary variable in one of the trials, while showing effects (or trends for an effect) on parameters that also showed significant effects with ESZ treatment compared to placebo.
- Other methodological problems are described in previous sections.

Other potential concerns were described in the study report, as in the following. Exploratory analyses for treatment sequence effects and treatment-by-baseline interaction effects are

described in the study reports. Treatment-by-baseline interaction effects were observed on some secondary variables and DSST, although, baseline scores were a covariate in the ANCOVA analyses. Missing data were not "imputed" and a last-observation-carried-forward approach was not employed for primary and secondary analyses.

B. Study 190-012: Effect of ESZ on Respiratory Drive in Healthy Male Adults.
Summary of the Study Design. The primary objective of this trial was to examine the effects of single oral doses of ESZ compared to placebo, on measures of respiratory drive in healthy males. A codeine treatment condition was included in this crossover study, as an internal control.

This trial was a single-center, randomized, double-blind, placebo-and active-controlled, four-way crossover trial conducted on a total of 14 generally healthy, 18 to 45 year old males. Subjects who smoked tobacco products were excluded from the trial. Subjects were randomized to a sequence of four of the following treatment conditions:

- 3 mg/30 ml solution of ESZ
- 7 mg/30 ml solution of ESZ
- 60 mg codeine sulfate tablet
- Placebo tablet or 30 ml solution

Subjects received each of the above single-dose treatment conditions at 9 a.m. on each of four study days. A 72-hour washout interval was employed in between each study day. Respiratory function was assessed on each study day using a spirometric rebreathing testing procedure at 45 minutes pre-dose, and at 2, 4, and 6 hours post-dose. Other safety assessments were also conducted which included 12-lead EKG at screening and at 1.5 hours postdose on each study day. Vital sign assessments were conducted at various time points, pre-and post-dose. Other safety assessments were included, as described in the protocol.

The primary respiratory drive measures were the following:

- Ventilatory Response to CO2
- Mouth Occlusion Pressure Response to CO2.

The slope of the change in each of these measures in response to the change in a partial pressure of CO2 was determined.

An analysis of covariance model was employed to examine treatment, sequence, subjects nested within sequence, and period main effects on each respiratory drive measure, using the baseline value on the given parameter as a covariate. Prior to conducting this analysis, a test for first order carryover effects was conducted using the 10% significance level. If significant carryover effects were revealed, than this variable would be included in the primary analysis. There were no missing data from 13 of 14 subjects who completed the trial (1 subject was withdrawn from the study due to a protocol violation).

Study 190-012: Summary of Results on Respiratory Drive Measures.
Table VIIB1 in the appendix summarizes the results (as provided by the sponsor). Neither of the ESZ treatment conditions showed significant treatment effects compared to placebo on Ventilatory Response as shown in Table VIIB1 Panel A in the appendix. A small decrease in Ventilatory Response was observed at two hours following codeine treatment ($p < 0.03$), with no significant effects observed at other time points. The baseline value (the covariate in the

ANCOVA model) was significant at 2, 4 and 6 hours post-dose for each respiratory drive parameter ($p<0.025$).

None of the active treatment conditions (ESZ treatment conditions or the codeine treatment condition) showed a statistically significant reduction in Mouth Occlusion Pressure Response compared to placebo with one exception (as shown in Table VIIB1). The exception was at 6 hours after receiving the lower ESZ dose in which a small reduction ($p<0.03$) was observed compared to placebo.

Other safety results (vital sign, reported AEs and others) were unremarkable.

Study 190-012: Conclusions

It is difficult to interpret the results on respiratory drive parameters in this study given that multiple comparisons were conducted on multiple parameters, at multiple time points and between multiple treatment conditions. The sponsor describes results based on comparisons between each active treatment group and placebo, while results on the overall ANCOVA for a treatment condition effect (other main effects) could not be found in the study report.

Another problem in interpreting the study results is that a crossover design was employed. The sponsor reports no significant first order carryover effects based on the initial analyses conducted by the sponsor on each of the parameters (determined for first order carryover effect was subsequently removed from the ANCOVA analysis). However, this analysis does not fully address the problems in interpreting results of cross-over trials.

Finally, the sponsor revealed a significant influence of the baseline value of the Ventilatory Response measure.

Given the above caveats, the trial generally did not reveal significant or remarkable treatment effects on impairment in either of the two primary respiratory drive parameters. Yet, the trial appears to have inadequate assay sensitivity for detecting a drug related effect. While, a small reduction in one of the parameters was observed at two hours after codeine treatment compared to placebo ($p<0.05$), a small reduction in the other primary measure ($p<0.03$) also occurred with a low dose of ESZ (and not with the other treatment conditions) compared to placebo at 6 hours post-dose (long after the known Tmax for ESZ). These observations appear more likely, to be spurious findings, given that a cross-over design was employed, that the observed group differences were small, at a level of significance that was only at $p<0.03$ or 0.05 (without correcting for multiple comparisons).

In conclusion caution must be given in interpreting the results of Study 190-012, such that one cannot conclude that the results demonstrate an absence of an adverse effect of ESZ treatment on respiratory drive. In the opinion of this reviewer, this study is a failed study, rather than a negative study for potential effects on respiratory depression. Yet, if such an effect were to exist, it would appear to be a small effect, at least on the parameters selected for this trial.

C. Study 190-015: Alcohol Interaction with ESZ in Healthy Subjects.

Summary of the Study Design. The primary objective of this trial was to examine potential interaction effects with coadministration of alcohol and ESZ on cognitive performance and on postural stability in healthy adults.

This four-way crossover, single-center, inpatient, double-blind, single-dose trial was conducted in generally healthy male and female subjects who were 21to 64 years old. Subjects had to score as a ≤moderate drinker on the Alcohol Dependence Scale to be included in this trial.

A total of 24 subjects were randomized to a treatment sequence such that each subject received each of the four treatment conditions:

- Placebo tablets plus alcohol-placebo
- Placebo tablets plus alcohol (0.70 g/kg)
- 3.5 mg ESZ and alcohol-placebo
- 3.5 mg ESZ and alcohol (0.70 g/kg)

Subjects received their assigned study drug with 240 ml of orange juice, after an overnight fast of approximately 10 hours. Subjects were not permitted to consume any alcohol for a 48 hour period prior to and after each clinic visit and were instructed not to consume more than five alcoholic drinks each week between visits. A 7-day washout period occurred between visits. Subjects underwent various safety assessments, as well as psychometric assessments.

The following computerized "cognitive" assessments were administered in the following order: Immediate Word Recall, Picture Presentation, Simple Reaction Time, Digit Vigilance Task, Choice Reaction Time, Tracking, Spatial Working Memory, Numeric Working Memory, Delayed Word Recall, Word Recognition, Picture Recognition, and Bond Lader Visual Analogue Scales of Mood and Alertness. Postural Stability was conducted as the last assessment in this battery. Parallel forms were used for each of the psychometric tests. Information and the rationale on selecting these tests could either not be found or was limited in the study report.

Psychometric data was analyzed by first subtracting the pre-treatment score from the post-treatment scores for each study day to determine the mean change from baseline on each parameter. Descriptive statistical analyses were conducted. Data from all randomized subjects was included in this analysis.

The sponsor used a "linear model" to determine treatment, sequence, and period main effects on the mean change from baseline to each time point on performance on each assessment, with subject nested within sequence as a random effect in this analysis (a SAS procedure PROC MIXED).

Study 190-015: Summary of Results.

A total of 22 out of the 24 randomized subjects completed the trial. One subject withdrew consent after Dosing Period II, and another subject discontinued due to a positive urine drug screen at the Dosing Period II visit.

See Figure VIIC1 in the appendix summarizing results on 10 parameters that were found to have significantly greater combination effects then individual effects (as provided by the sponsor). Upon visual examination of these figures, ESZ treatment appeared to be associated with impairment on most the parameters listed below, with the greatest numerical decline in performance at one-hour post-dose (from baseline performance) that generally diminished over time:

- Numeric Working Memory-Speed
- Spatial Working Memory-Sensitivity Index

- Immediate Word Recall-Percent Words Recalled
- Word Recognition-Sensitivity Index
- Picture or Recognition-Speed
- Power of Attention
- Quality of Secondary Memory

The mean change in each of the above parameters was numerically the greatest in the concomitant alcohol-ESZ treatment condition compared to other treatment conditions (placebo, ESZ alone, and alcohol alone). Self-Rated Calmness also showed significantly greater combination-treatment effects than individual-treatment effects. However, examination of the results in Figure VIIC1 reveals that mean changes varied inconsistently over time, suggesting that results are due to artifact.

Additional safety results of this trial are described in the following. None of the subjects had SAE's or were adverse dropouts. Reported AE's generally failed to reveal any unexpected findings with some possible exceptions. As is expected for this drug class, alcohol intolerance was reported in 9% of subjects in the placebo/alcohol treatment condition compared to a greater incidence of subjects after the ESZ/alcohol combination treatment (26%), while the incidence in other treatment conditions was 0%. Most of these AE's were described in brief narratives. Most subjects with alcohol intolerance reported as an AE are described in the narratives were generally associated with an earlier onset and a prolonged duration of CNS AE's (AEs of intoxication) in the ESZ/alcohol condition compared to the alcohol-alone condition. In other subjects reported to have alcohol intolerance, AE were reported during the ESZ/alcohol condition and not in the alcohol-alone condition. Confusion and depression were each reported in one subject during the ESZ/alcohol condition.

One 22-year-old male with an unremarkable medical history who was reported to have alcoholic intolerance (as an AE) also had marked elevations in ALT and AST levels (up to approximately a 10-fold increase from baseline) and marked elevation in CPK associated with muscle soreness after a fall. Elevations were first revealed one day after the final treatment condition. The final treatment condition given to this subject was the alcohol/ESZ combination treatment. Both ALT and AST levels peaked two days later to values of 176 U/L (0-47 U/L WNL) and 385 U/L (0-30 U/L), respectively. Upon repeat testing, levels declined and eventually normalized within approximately 12 days (LFTs were conducted every two days over this period). Baseline laboratory results that were considered abnormal or clinically significant (ALT and AST were within normal limits at screening). This subject also complained of muscle soreness about six hours after his last treatment and had fallen on his bed hitting his chest. CPK levels were dramatically elevated on the first assessment conducted four days after his final treatment in which levels reached 11270 IU/L (35-232 IU/L WNL), but declined over time and eventually returned to normal. Elevated CPK appeared to be associated with muscular injury associated with the patient's fall after dosing and the fall was likely to be drug-related (alcohol/ESZ). The LFT results could be reflecting an effect of two treatment conditions of alcohol. A possibility is that this subject was abusing alcohol, between study visits, but not reporting it and suffered alcoholic hepatitis. However, an effect of ESZ or the combination of the study drug with alcohol on liver function tests cannot be ruled out.

Study 190-015: Conclusions.

The study has a number of limitations from a methodological perspective impacting on the interpretability of the results. Firstly, the rationale for selecting specific psychometric measures (including a discussion of psychometric properties such as reliability, validity, potential practice effects and others) could not be found in the study report. References for each test and references with data to support conclusions about the utility of these tests for meeting study objectives could not be found. Another limitation, as noted by the sponsor, is that numerous statistical comparisons were conducted (e.g. a total of 144 interaction comparisons were made in addition to others), such that the potential for making a Type II error is of concern.

Despite, these and other limitations, a significant combination ESZ/alcohol treatment effect was observed on primarily memory-related tests, and tests that are dependent on attention and speed. These observations appear to reflect a real combination effect (ESZ/alcohol) for several major reasons. Firstly, observations were in the direction that would be predicted, with greater impairment following combination treatment compared to other treatment conditions (alcohol alone, ESZ alone or placebo treatment) and in most cases in a direction predicted for each mono-treatment condition (i.e. ESZ alone and alcohol alone, conditions). Placebo treatment generally showed either improvement over time suggestive of practice effects or little, to no change. Secondly, impairment with combination treatment or mono-active treatment (particularly with alcohol alone treatment) was time-dependent, in that the observed effects generally peaked near Tmax and diminished over time, thereafter, as would be predicted if effects were drug-related. However, results on Self-Rated Calmness were inconsistent over time and across treatment groups, such that observations on this parameter were likely to be artifactual.

A discussion about potential practice effects on test performance, cannot be found in the study report, as the test battery was administered on multiple time points on a given study day and on multiple study days (a total of four study days). One concern is that the results as described by the sponsor may be an underestimation of the potential adverse effects on test performance. That is, a potential drug effects on impairment on a learning curve associated with practice effects may exist, but may not be revealed in the statistical methods employed in the trial. Therefore, potential adverse effects on psychometric performance were not adequately examined in the study.

It is important to note that the study report does not describe results on parameters showing significantly greater impairment with ESZ treatment given alone, compared to placebo treatment on psychometric measures. The following observations regarding the ESZ treatment condition are noted and are based on visual examination of Figure VIIC1 showing results of parameters that the sponsor chose to describe in the study report (the parameters that showed significant effects with combination treatment). ESZ mono-treatment showed greater impairment than placebo on several parameters (Numeric Working Memory, Immediate Word Recall, Word Recognition, Picture Recognition, Power of Attention, and Quality of Secondary Memory). This impairment was time-dependent in that impaired performance was greatest near the anticipated Tmax for ESZ and diminished over time, while little to no impairment was observed after approximately four to eight hours after treatment. Therefore, it is important to determine if a similar impairment was observed with other parameters (e.g. performance speed, attention, motor function among others). In conclusion, these observations provide evidence for adverse effects of ESZ appears on memory function, as well as on other on other aspects of psychometric performance.

Results on postural stability were not described in the study report, other than that this parameter did not show significant combination treatment effects on performance. Since, impairment on performance may be anticipated following treatment with ESZ, alone, as well as after treatment with alcohol, alone, a description of these results would be useful.

VIII. Integrated Safety Information

A. Background Information

1. Safety Information Provided in the ISS of the Original Submission. Safety data was integrated across ESZ studies within each of the following study-type categories in the ISS (Table VIIIA1 in the appendix enumerates subjects in each trial):

- Daytime (1-7 days) Phase I studies in healthy volunteers: Studies 190-001, -002, -005, -010, -011, -012, -015, -018, -019, -020, -021, and -023. One of these trials (-005) was conducted on elderly healthy adults while other trials were generally conducted on young male and female adults (most were younger that 40 years old).
  This does not include Phase I studies involving:
  - Special populations (190-13, -014 and –016 on hepatically or renally impaired subjects or on subjects with a history of benzodiazepine abuse, respectively)
  - Concomitant treatment: 190-022
- Nighttime (1-7 days) studies in Non-Elderly Adult healthy volunteers: Studies 190-024 and 190-026
- Nighttime (1-7 days) studies in Non-Elderly Adult patients with Primary (Chronic) Insomnia: 190-025 and 190-045
- Nighttime 2-week studies in Elderly patients with Primary (Chronic) Insomnia: 190-047 and 190-048

Non-integrated safety data from each study was provided in Study Reports for each individual study.

Non-integrated safety data was provided in the ISS for the following large Phase III studies which were longer term studies:

- Nighttime 6-week study in Non-Elderly patients with Primary (Chronic) Insomnia: 190-046
- Nighttime Longterm study in Non-Elderly patients with Primary (Chronic) Insomnia: 190-049

See Section IV.B. and tables of trials in this previous section (Tables IV.B.1.a-c) for overall study design and numbers of subjects in each trial. See Table VIII.A1 in the appendix for the enumeration of the ITT Safety Population for each study and for each integrated study type.

Chronic Insomnia trials in elderly patients consisted of two 2-week trials (190-047 and 190-048). As shown in Table IV.B.1c. (in Section IV.B of this review), these trials had 228 ESZ completers.

All trials in the submission were completed (no ongoing trials).

2. Safety Information Provided Elsewhere

Some safety information that is typically included in the ISS of a submission could not be found in the ISS, but were sometimes found in the Study Report of a given trial as described in sections below. The majority of results on clinical assessments in the ISS were based on data that was

primarily collected after cessation of double-blind treatment (e.g. days to weeks post-treatment) rather than showing results in which only the on-treatment data was included in the analyses (e.g. at treatment endpoint and on each study visit during the double-blind treatment phase compared to pre-dose/baseline values). This deficiency of the ISS was raised with the sponsor at pre-filing.

In response to some other problems regarding the ISS that were raised with the sponsor during prefiling, the sponsor provided results of safety data using some on-treatment data from selected trials in their 120-Day Update Report. These results are described in subsections below, as specified.

Subsections below also include additional safety results on a re-analyses of AEs from the 120-Day Update Submission (as specified).

The Update report submission did not show results of analyses of any new data, as all trials in the original submission were completed (no ongoing trials).

3. Safety Information on Zopiclone

Information on zopiclone (the racemate) was provided in submissions under this NDA and is under review by the Safety Group in the Division, since most of this information is postmarketing data. Because of some evidence for effects of the study drug on testicular function in preclinical trials (as described in personal communication with the Preclinical Reviewer, Dr. Atkrachi), the results of a zopiclone trial that examined parameters a testicular function in males, is described in this review. Other safety information on zopiclone were not reviewed by this reviewer (because they were under review by the Safety Group, some trials examined safety measures similar to those in ESZ trials, or were results or descriptions of results that were not considered by this reviewer as interpretable or meaningful).

B. Demographic Characteristics

Demographic features of subjects in Efficacy trials (190-025, -45, -46, -047, -048, -049) and Special Safety Trials (Studies 190-012, -015, -024 and -025) were previously described under Sections VI-VII. Most Phase I trials were conducted on young healthy adults who were primarily Caucasian.

C. Extent of Exposure

Overall exposure by ICH Guidelines and in Patient Years:

ICH Guidelines were met for exposure at dose levels of ≥ 3 mg (3 mg is the proposed recommended daily dose) as follows (the number of subjects required by ICH guidelines is provided in the parentheses):

- Overall exposure (1500 subjects at single or multiple doses per ICH guidelines): 1076 subjects (ITT Safety population)
- 6 month exposure (300-600 subjects per ICH guidelines): 360 completers during the double-blind phase of Study 190-049 (593 ITT Safety subjects)
- 1 year (at least 100 subjects per ICH guidelines): 296 completers in Study 190-049 (these subjects were among the 360 subjects above who completed 6 months of double-blind ESZ treatment).

Exposure expressed in patient years could not be found in the submission. This information, as well as other information, that could not be found in the submission

were itemized in the 74-Day letter dated 4/14/03 (Clinical items 1-4 in the letter). The information on exposure under item 4, as well as information specified in items 2 and 3 in the letter could not be found in subsequent amendment submissions.

The following describes the information on exposure that could be found in the original submission. Among subjects in the Safety Population, a total of 1839 subjects received at least one dose of at least 1 mg of study drug and 1206 subjects received at least one dose of 3 mg or above of study drug as shown in Table VIIIA1 (in the appendix). This table enumerates subjects of the ITT Safety population by dose-level and by duration at each dose-level, in each category of integrated studies (as provided by the sponsor). Table VIIIC1 in the appendix provides the average daily dose within each dose-range category for each subset of integrated trials.

Section IVB of this review and Tables IVB1a-c (located in Section IVB) enumerates completers, as well as subjects of the safety population in the trials. As shown in the summary tables, each trial generally had over 90% of subjects in the ITT safety population who were completers, except for the long-term trial, Study 190-049. In this longer term trial approximately 60% of subjects in the ITT safety population were completers are the six-month double-blind phase, of which most of these subjects (approximately 80%) completed the six-month open label 3 mg ESZ extension phase of the trial.

D. Deaths

No deaths were reported among ESZ treated subjects (out of approximately 1839 ESZ treated subjects). Two deaths (involving myocardial infarction) occurred either, during screening, or during placebo treatment (in Studies 190-048 and 190-049).

E. Serious Adverse Events (SAEs)

See Tables VIII.E.1-3 for a listing of SAEs for all studies (for Integrated Studies, The Open-Label Phase of Study 190-049, and Non-Integrated Studies in each table, respectively, as provided by the sponsor).

Short-term studies (Days 1-7, nighttime or daytime studies).

None of the short term nighttime or daytime studies (1-7 day trials) that were integrated in the ISS had SAEs. SAEs were not reported in any of the non-integrated studies, as well, except for 1ESZ S (listed in Table VIII.E.3) in a small Phase I Study 190-013 examining the effect of impaired hepatic function on PK. This subject was in the normal hepatic function group of this trial who had gastroenteritis.

2 to 6-Week Chronic Insomnia Studies (2-week Elderly Trials and a 6-Week Non-Elderly Adult Trial).

As shown in Tables VIIII.E.1, a few SAEs occurred in the 2-week Studies 190-047 and –048 in elderly subjects with Chronic Insomnia (subjects with SAEs were 2 out of 208 ESZ subjects; 1%, and 2 out of 315 Placebo subjects; <1%). Yet, no SAEs were reported in a longer term (6-week) study in non-elderly patients with Chronic Insomnia (Study 190-046).

One elderly S (S427004 in study 190-048) who had several cardiac-related events that included an SAE of chest pain. This subject is described in Table VIIIE4 in the appendix.

6-Month Double-blind/6-month Open-Label Study 190-049 in Non-Elderly Adults with Chronic Insomnia

The longer term trial, a 12-month study (Study 190-049) had the most SAEs among all shorter-term clinical trials. The following enumerates the total number of subjects with SAEs in each treatment phase of Study 190-049 (with the incidence in parentheses):

- 6-month double-blind phase: 17 SAE's out of 593 ESZ subjects in the Safety Population (2.9%), 2 SAE's out of 195 Placebo subjects in the Safety Population (1%)
- ESZ Open-Label extension phase: 11 SAE's out of 471 subjects in the Safety Population (2%).

Table VIIIE1-2 lists all SAE's reported in the study. A description of ESZ subjects with SAEs of enlarged uterine fibroids during both phases (the double-blind and open-label phases) of this longterm 12-month study is provided later in this section.

Common SAE's in the Double-blind Phase of Study 190-049. The following SAE's were types of SAE's were the most common SAEs in the 6-month double-blind phase of Study 190-049 were the following (sample sizes of Safety populations were 195 Placebo subjects, and 593 ESZ subjects at a 3 mg daily dose level):

- **Psychiatric-related** SAEs (4 ESZ subjects; 1% and no Placebo subjects; 0%): 2 subjects had agitation as the SAE (0415007, 0443005), 1 S had overdosed on ESZ (S0087013) and the fourth S (0471021) had "neurosis" as an SAE but was also reported to exhibit hostile behavior. All subjects but the S with overdose, had a history of psychiatric illness or a history of similar events. While pre-existing psychopathology was reported in 3 of the 4 subjects, one cannot rule out a potential role of study drug.

  The fourth S (overdose) did not allow release of her records to the sponsor and information on this subject was limited, as described in the narrative. The S ingested an estimated amount of 18 to 36 mg of ESZ on her first day of treatment. The etiology of this event is unclear. She was a 27 year old female who could have had underlying psychopathology. However, in the absence of more information, a role of the study drug cannot be ruled out.
- **Chest pain** (3 ESZ subjects; 0.5% and 1 Placebo S; 0.5%). 2 ESZ subjects (0317033, 0448024) with chest pain had pre-existing cardiac conditions[5] or risk factors (the latter S had atypical chest pain and a negative work-up for cardiac or gastrointestinal conditions and restarted open label ESZ treatment taken over 6-momths after the SAE). The former S (0317033) voluntarily withdrew from the study 5 days after his chest pain resolved.

  The etiology of the chest pain in the third ESZ S (0439001) is unclear, but did not appear to be a cardiac event based on information in the narrative. This S had atypical, intermittent chest pain unresolved with nitroglycerin. The S was hospitalized. Cardiac enzymes, ECG and two stress tests yielded results that were within normal limits. The chest pain resolved and the S withdrew from the study (last dose of ESZ was on the day when the event began).

[5] S0317033 had a history of bypass surgery and myocardial infarction, two angioplasty procedures, diabetes, and other risk factors.

- **Gastrointestinal (GI) disorder or GI related SAEs** (4 ESZ subjects; 1% and 1 Placebo S; 0.5%): These events were probably not drug-related since pre-existing conditions appeared to exist, or the conditions were chronic, or the SAE's were not atypical of the general population (appendicitis occurred in 2 of the ESZ subjects). These ESZ subjects completed the study following their events.[6]

SAEs of Uterine Fibroids, Enlarged During the Double-blind and Open-Label Phases of Study 190-049. Enlarged uterine fibroid SAE's occurred in a total of 3 ESZ subjects and no placebo subjects in both phases of the trial as follows:

- Double-blind Phase: 1 ESZ S (out 593 subjects) and no placebo subjects (out of 195 subjects).
- Open-Label Phase: 2 subjects (out of 471 subjects).

These subjects underwent hysterectomy (also bilateral oopherectomy in S0456007) resulting in at least a temporary cessation of ESZ treatment. Because one of these subjects (0409009) discontinued double-blind treatment and withdrew from the study she is described later (she withdrew 4 days before her "elective" surgery).

Since these 3 ESZ subjects had pre-existing conditions and/or risk factors,[7] a potential relationship of study drug may be unlikely. Yet, one cannot be certain that they developed new tumors *de novo* (during treatment) or that their condition worsened with treatment. The narratives do not provide clear objective descriptions of the course of their condition over time during treatment (based on diagnostic tests or other objective measures). For example, the narratives do not describe how the number of tumors or the size of the tumors may have changed, by conducting serial imaging (or using imaging results prior to study entry compared to imaging at the time of the SAE), or how the frequency or severity of symptoms may have changed using objective assessments (i.e. by having subjects keep daily logs). See verbatim taken from the narrative on the ESZ subject of the double-blind phase, below, as an example of the information provided in the narratives. The preferred terms for these SAE's did not include "enlarged" tumors but simply refer to the disorder (e.g. fibroid tumors) as shown in Table VIIIE2.

One S ((0458007) was reported by the investigator as showing no worsening of her condition from baseline. However, it is not clear from the narrative how this was determined (or if it was determined by objective measures and other details).

A description of the subject with enlarged uterine fibroids in the double-blind phase of the trial used described in detail below. The 2 subjects in the open-label phase are described in Table VIII. E.4 in the appendix on selected SAEs in the trials.

A Description of Subject 0409009 with the SAE of Uterine Fibroids Enlarged in the Double-blind-Phase in the Esopiclone 3 mg treatment group (the following is verbatim from the narrative on p.316 of the ISS.pdf):

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[6] GI-disorder SAEs: 2 ESZ subjects (0439026 and 0093025) and 1 Placebo S (0472011) with GI disorder had appendectomies. 1 ESZ S (0317030) had an SAE of abdominal pain and had abdominal adhesions found on laparoscopy who had a history of diverticulitis and heartburn. A fourth ESZ S (0462002) had cholelithiasis (who had risk factors, history of indigestion, with diagnosis of chronic cholecystitis on pathology, and completed the 6-month open label phase after cholecystectomy).

[7] All 3 subjects were between 44 to 55 years old and had pre-existing conditions and/or risk factors (perimenopausal or postmenopausal irregular heavy and painful menstrual bleeding, taking hormonal replacement therapy, and others) or had a history of fibriods.

S 0409009: *This subject was a 48-year-old Caucasian female. The subject was perimenopausal-menopausal and reported having irregular painful, heavy menstrual periods (ongoing since August 1996). She was scheduled to have an elective hysterectomy for uterine fibroids on — — She was randomly assigned to receive esopiclone 3 mg on 07 May 2001. The subject had surgery on — (as scheduled) for uterine fibroids enlarged ("uterine fibroids"). The event was severe, serious, and the relationship to treatment was not related, and the subject was discontinued. The date of last dose was 04 October 2001 and the date of last contact with the subject was 29 November 2001. (Reference: CSR 190-049; IND Safety Reports submitted on 21 November 2001 [Serial No. 071] and 21 February 2002 [Serial No. 081].)*

6-month Open Label ESZ Treatment Phase of Study 190-049

Uterine Fibroids, Enlarged. This SAE was reported in 2 subjects out of 471 subjects in the Safety population (all subjects in the open-label phase were receiving ESZ treatment at the 3mg daily dose level). These subjects were described in the previous section (also in Table VIIIE4 of selected SAEs). Table VIIIE2 shows all SAE's reported during the open-label phase of the trial. These SAE's are generally not unexpected for the population and given that subjects were undergoing multiple assessments over a 12-month period. This phase of the trial did not employ a placebo control group for comparison, which limits the interpretation of the results on SAE's reported during the open-label phase of the trial.

Other More Common SAEs Among All Studies Combined (not previously described).

As shown in Tables VIIIE1-3 in the appendix, accidental injury occurred in several subjects that were probably not drug-related. This conclusion is based on either of the following reasons or combination of reasons: the nature of the event (as described in narratives), the time of dosing relative to the event (some events occurred several days after treatment), the overall incidence of the SAE did not show a predominance towards ESZ compared to placebo subjects in a given trial or among the trials, combined.[8] Other common SAE's, were previously described, and occurred primarily in the long-term trial (Study 190-049).

F. Dropouts due to Adverse Events

See Tables VIII.F.1-3 for an enumeration of the adverse dropouts (ADOs) categorized by Preferred Term AEs among the trials (except for a non-placebo controlled open-label phase of Study 190-049 in which ADOs are discussed below). Subsections below describe overall results on ADOs for each study-type category of these trials.

Adverse Dropouts (ADOs) in Short-Term Integrated Trials in Non-Elderly Adults (1-7 Daytime or Nighttime Studies).

No ADOs were reported.

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[8] Accidental injury (reported as an SAE) occurred primarily in the long-term study 190-049 as follows: a total of 3 ESZ subjects and no placebo subjects during treatment phases, 1 Placebo S and a ESZ S over 30 days post treatment. This SAE was reported in 1 ESZ S and 0 Placebo subjects in a 2-week study of elderly Chronic Insomnia patients (Study 190-047). These SAE's were primarily associated with work-related events or events that were probably not drug-related as follows: had a heavy object fall on a limb, injury with heavy lifting, and others, the event occurred after 2 days in a subject (169714) with risk factors for falling or the injury occurred over 30 days after treatment (0416001).

Adverse Dropouts (ADOs) in Short-Term Integrated Trials in Elderly Adults with Chronic Insomnia (2-week Studies, 190-047 and 190-048).
The overall incidence rates of ADOs were 1.9% of ESZ subjects and 3.8% of Placebo subjects. Table VIII.F.1 in the appendix shows the following events that occurred in more ESZ subjects than placebo subjects, while noting that the incidence in ESZ subjects for a given AE term did not exceed 1%:

Diarrhea	Ataxia
Nausea	Dizziness
Pruritus	Vertigo
Somnolence	

These events are generally not unexpected for the drug class, for clinical drug trials or for the study population.

Adverse Dropouts (ADOs) in the 6-week Study in Non-Elderly Adults with Chronic Insomnia (190-046).
Table VIIIF2 in the appendix shows the incidence of ADO's in Study 190-046. ADOs in this study did not reveal any remarkable AEs or events that appeared to be clearly drug-related. The few events that occurred were in the low dose ESZ group (a 2 mg bedtime dose level, N=104) and not in the high dose ESZ group (a 3 mg bedtime dose-level, N=105). However, a possible drug-relationship for these ADOs may be considered given that none of the placebo subjects (among 99 Placebo subjects) were ADOs compared to 1% of the ESZ subjects (low and high dose groups, combined). The incidence of the ADOs by AE Preferred term in the low dose ESZ group (2 mg ESZ group) was as follows: headache (1.9%), nausea and vomiting (each in 1% of subjects).

ADOs in the Longterm Study 190-049 in Non-Elderly Adults with Chronic Insomnia
<u>6-Month Double-blind Phase of Study 190-049 (3 mg group; N=593 and placebo; N=195).</u>
As shown in Table VIII.F.3, 13% of ESZ subjects and 7% of Placebo subjects were ADOs during the double-blind study phase.

A description of specific ADOs other than a table of the incidence of ADOs by Preferred AE Terms cannot be found in the ISS for either the Double-blind phase or the Open-label phase of this large longterm safety study. However, narratives were provided that included additional information.

Some ADOs were not unexpected, either for the study drug or drug class, for the study population, or for clinical drug trials (e.g. unpleasant taste, erythema multiforme in 1 ESZ S, pruritis or rash in 4 ESZ subjects, blurred vision or dizziness, asthenia, somnolence, nausea, abnormal thinking, sleep walking in 2 ESZ subjects, among others). Other ADOs were not likely to be drug related.

Narratives of some of the ADO's had limited information, whereby it was difficult to determine whether or not the events were drug-related, such as the following ADO's. One S (S0317045 had mild to moderate elevations in liver enzymes (Preferred Term was "liver

damage") resulting in an ADO.[9] Another S (S04007044) had chest pain resulting in treatment cessation. Since the narratives provide no other information regarding the event or regarding any diagnostic tests, one cannot determine the likelihood that these ADO's could be drug-related.

Abnormal thinking which occurred in 3 ESZ subjects and no Placebo subjects included the following descriptive terms: impaired cognition, difficulty concentrating or "abnormal thinking." None of the Preferred terms or descriptive terms in the incidence summary table or line listing were hallucinations and there were 2 ESZ subjects (no Placebo subjects) with ADOs of memory impairment. A section later in this review focuses on AEs of hallucinations and memory impairment. ADOs of special interest (AEs are serious in nature and/or more common with greater frequency in ESZ subjects compared to placebo subjects) are described in a subsection, below.

One noteworthy observation, that is not described below, is that ADOs of unpleasant taste was reported in 10 ESZ subjects and only 1 Placebo S as the either the only AE that resulted in discontinuation of the study drug, or was reported with other AEs resulting in study withdrawal.

ADOs of Special Interest in the 6-month Double-blind Phase of Study 190-049 ADOs described in this section were selected (by this reviewer) for one or several of the following reasons: the ADOs were more common (generally did not occur in any placebo subjects, but occurred in several ESZ subjects), were particularly serious in nature, and/or were of interest based on preclinical findings.

Examination of Table VIIIF3 in the appendix, which shows the incidence of ADOs by Preferred Term in each treatment group, revealed the following events of special interest during the double-blind treatment phase. A few ADOs as specified below were of subjects with AEs during double-blind treatment that ultimately lead to termination of treatment during the open-label phase and a few other ADOs occurred only during the open-label treatment phase (these ADOs are clearly specified, as such).

Neoplasia.

While none of the 195 Placebo subjects (0%) were ADOs for events of neoplasia, 3 (and possibly more as described below) of the 593 ESZ subjects (0.5%) were ADOs during the double-blind treatment phase due to the following respective events (Preferred Terms per narratives):

- Hepatic Neoplasia in S0450024 who appeared to develop multiple tumors in multiple organs and tissues: the breasts, lung, kidney and liver (based on mammography, ultrasound and abdominal and chest CT scans). This obese (236 lbs) 43 year old female smoker had a previous history of a normal mammogram and pap smear (approximately one year or less prior to starting double-blind treatment). Approximately one year prior to treatment she had a hysterectomy for endometriosis and ovarian cysts. See the narrative below (under the narrative subsection), describing the chain events before, during and after double-blind treatment. This ADO may be drug-related.

[9] The narrative of this S0317045 only describes an elevation in liver enzymes (ALT and AST) observed at baseline and screening that increased during open-label treatment (from 106 at baseline to 167 on treatment) resulting in an ADO (no mention of any additional diagnostic tests).

- Breast Neoplasm in S 0406001 in a 57 year old Caucasian female with no history of medical conditions (and appeared to take no concomitant drugs) who experienced a "lump" in her left breast after approximately 1 ½ months of double-blind treatment. It was considered "benign" but it is not clear how this was determined (no mention of biopsy). However, ultrasound and mammography were conducted (results not described). The menopausal status of this S and the subsequent course of her breast tumor over time is not described (study drug was discontinued upon discovery of the "lump"). This event could be drug-related.
- Neoplasm in S 0421004 in a 62 year old female with no medical problems at screening who had a "nodule in throat" after approximately 5 months of double-blind treatment that resolved 10 days after cessation of treatment. The narrative provides no other information (e.g. if any diagnostic tests were conducted). This event could be drug-related.

It is not clear why the above ADOs of neoplasia were not reported as SAEs.

Subject 0398013 was reported to have thyroid disorder as an adverse event leading to treatment discontinuation during the open label phase of the study. This subject was described as having "nodule on the left side of the thyroid." It is not clear if this nodule was further assessed. Therefore it is not clear if the nodule reflects the presence of neoplasia.

Uterine fibroids enlarged in S 0409009 that lead to termination of treatment were previously described under Section E on SAEs. It is not clear of the diagnosis of uterine fibroids was confirmed by histopathological examination of tissue following the hysterectomy in this subject or in others with SAE's of enlarged uterine fibroids (see Section on SAEs).

Gynecological-related ADOs.

No placebo subjects (0%) and 6 ESZ subjects (1%) had the following events leading to ADOs listed under urogenital body system (except "cyst" below was listed under "Body as a Whole") during the double-blind treatment phase of the study:

- Breast neoplasia (see above)
- Uterine fibroids, enlarged which was also an SAE (see above)
- Metrorrhagia in S 0460013 who was a 29 year old female with had "interrupted menstrual flow" approximately 10 days after starting double-blind treatment that "resolved" 5 days later. Study drug was discontinued due to multiple AEs that included metrorrhagia among others (abdominal pain, asthenia, anorexia, diarrhea, headache, ecchymosis, abnormal thinking/difficulty concentrating, rash and others). This S had no medical history or concomitant medications that would explain her disruption of menses. The outcome of subsequent menstrual cycles after resolution of this event and after treatment cessation is not described in the narrative. The metrorraghia could be drug-related.
- Breast Pain in S 0421013 who was a 60 year old female with a history of fibrocystic disease who developed breast pain after about 24 days of double-blind treatment that resolved approximately 4 days after cessation of treatment. This shows a time course suggestive of a relationship to study drug.
- Cyst which was an "ovarian cyst" occurred in S 0432002 after about 2 ½ months of double-blind treatment (diagnosed by ultrasound) leading to the ADO. This S was a 35 year old Caucasian female with no medical conditions at screening and no concomitant drugs

described in the narrative. There is no other information or follow-up information described in the narrative. This event could be drug-related.

Endocrine System ADOs. Some of the previously described events could be endocrine related (e.g. some of the gynecological ADOs). The following describes ADO's listed under Endocrine System ADO is in the summary Table VIIIF3 in the appendix.

One placebo S and one ESZ S had hypothyroidism leading to an ADO during the double-blind treatment phase. An additional S (S0398013, previously described above) was a 61 year old female (healthy at baseline) participating in the open-label phase of the trial, who discontinued ESZ treatment due to "thyroid disorder" ("nodule on the left side of the thyroid") after approximately 7 months of treatment (6-months double-blind ESZ and approximately 1 month of open-label ESZ).

Psychiatric-Related ADOs.
The following psychiatric related AEs leading to ADOs (listed under Nervous System AEs) were observed among a total of 22 ESZ subjects (3.7%) compared to no placebo subjects (0%) based on data from Table VIIIF3 (in the appendix) during the double-blind treatment phase (unless otherwise specified):

- Depression in 12 subjects (2%) and Emotional Lability in 2 subjects (0.3%). An additional ADO of emotional lability started during double-blind ESZ treatment but treatment was not terminated until the open-label phase (in S0428012).
- Depression in 1 S leading to discontinuation was listed as having depression more than 14 days after treatment (S 049-256-004) in Listing 4.3.3 in the ISS. Apparently this S did not continue on to the open-label phase and was therefore identified as an ADO.
- Overdose in 1 S (0.2%) which was also an SAE (in S 087013 who was previously described in section E)
- Anxiety in 5 subjects (0.8%) and Nervousness in 1 subjects (0.2%). 2 additional subjects had anxiety during double-blind ESZ treatment but discontinued treatment during the open label phase (S0448027, S0416016). One of these subjects had "increased irritability."
- Agitation in 4 subjects (0.8%) and Hostility in 1 S (0.2%). 2 of the subjects with agitation were coded as SAEs and also had panic attacks and/or disorder (S415007 and S443005) who were previously described.
- Neurosis in 1 S (0.2%) which was also an SAE in S 471021, who was previously described.

Some subjects had several of the above AEs leading to an ADO such that some of the above enumerated subjects are counted more than once across AEs. However, the total number of subjects with any one of these AEs, or any combination of the AEs, was 22 ESZ subjects, as previously described.

Additional Psychiatric-related ADOs during Open-label Treatment were:

- 2 subjects with Anxiety and 1 S with depression

Other Nervous System ADOs.
Dizziness and memory impairment resulting in ADOs occurred in 4 (0.7%) and 2 (0.3%) ESZ subjects for each AE, respectively, compared to 1 (0.5%) and no (0%) placebo subjects for each event, respectively.

As previously described, 3 ESZ subjects and no Placebo subjects had "abnormal thinking" with the following descriptive terms reported in each subject, respectively: impaired cognition, difficulty concentrating or "abnormal thinking." An additional S with abnormal thinking ("difficulty concentrating") among other AEs resulted in an ADO during open-label treatment. Also 2 ESZ subjects (no placebo subjects) had sleepwalking leading to study withdrawal.

Selected Narratives of ADOs of Special Interest (verbatim from Section 16.1.13.3).

Hepatic Neoplasia: ***Subject 0450024 [Double-blind Esopiclone 3 mg]: Neoplasm (2 events; possibly related); Hepatic Neoplasia (possibly related)***

This subject was a 43-year-old Caucasian female who was randomly assigned to receive esopiclone 3 mg on 18 May 2001. She had a reported history of lumps in her left breast (in —) and ovarian cysts(in —); she had a hysterectomy in — (endometriosis and ovarian cysts). She was53 inches and 236 lb at study entry. She had a mammogram in — and Pap smear in — which were within normal limits. Smoking history indicates that she was a smoker for 28 years (1.5 packs/day) and stopped smoking on 06 March 2000. There was no history of alcohol or drug abuse.

At study entry, the findings and impression of the subject's bilateral mammogram were as follows. Small fairly well-defined nodular densities in both breasts had become less prominent since the earlier outside mammograms. There were no new or suspicious masses, clustered microcalcifications, skin or nipple changes. The Bi-Rads Category 2 had a benign finding. The nodular densities in both breasts were benign. The one on the right had resolved since earlier films. At study entry, the findings and impression of the subject's left breast ultrasound were as follows: The two small nodular densities seen on the mammogram were not identified ultrasonographically. No identifiable mass was seen with ultrasound. Therefore, they were considered solid. The masses, however, had remained stable on mammographic criteria consistent with a benign etiology.

An abdominal CT scan was performed on — which revealed nodules on the right kidney (preferred term: neoplasm), right lung (preferred term: neoplasm), and liver (preferred term: hepatic neoplasia). The subject's ALT was 42 U/L at screening, but was found to be elevated to 52.0 U/L (ULN=47.0 U/L) on — and 54.0 U/L on — The CT scan findings prompted the Investigator to discontinue the subject from further participation in the study (study drug was discontinued on 09 November 2001). An Early Termination visit was performed on 15 November 2001. The physical examination at this visit was within normal limits. There were no adverse events/symptoms described by the subject at that visit. The events were moderate, not serious, the relationship to treatment was possible, and the subject was discontinued.

Further follow-up for this adverse event was obtained after the subject was discontinued. A follow-up chest CT scan performed on — revealed that there was a nonspecific 4 mm soft tissue nodule in the right lower lobe which appeared well-circumscribed but with no evidence of calcification. No additional nodules were identified, and there was no evidence of hilar or mediastinal adenopathy. Intra-abdominal structures were unremarkable as visualized. The nodule appeared slightly larger than a preceding CT scan of the abdomen, which included the lower thorax. There was an apparent slight interval increase in size that may have been due to a slight difference in patient positioning.

— another follow-up CT scan of the chest was performed with IV contrast with images compared to a prior CT of the chest dated — and a prior CT abdomen, which showed the small nodule at the right lung base, dated — . The nodule in the right lower lobe was unchanged compared to the most recent CT of the chest. It actually appeared slightly smaller, but this may have represented a slightly different slice selection, clearly there was no progression. In — , an MRI of the spine was performed. Only postoperative changes from the spine fusion surgery (cervical) were observed. (References: Appendices 16.2.1.1, 16.2.1.2, 16.2.2, 16.2.5, 16.2.8, 16.2.12, 16.2.24, 16.2.25, and 16.2.33; Data on file with Sponsor.)

ADOs during the 6-month Open-Label ESZ Phase of Study 190-049.

This subsection describes additional ADOs during the open-label phase of the study that were not among ADOs of special interest (described above). These additional ADO's include the

following and generally failed to reveal any remarkable or unexpected events (for the study population, for the study drug or for the drug class): atrial fibrillation (an SAE in an elderly S with a positive history for syncope and hypertension), hemoptysis ("spit up blood" in a 39 year old female with negative chest x-ray who had other AEs of asthenia, "difficulty concentrating" and nausea resulting in the ADO), hepatitis (later diagnosed as hepatitis B), cardiovascular disorder ("regurgitation of heart valves" in a 23 year old female), unpleasant taste in 2 subjects of which 1 S had dizziness, insomnia and headache, as well.

Dose Dependent ADOs in Clinical Trials

The trials below are multiple dose trials in patients with Chronic Insomnia that employed an ESZ multiple, dose-ranging, parallel group design.

In the 6-week non-elderly trial, 190-046 the following ADOs showed an incidence of at least 1% in a ESZ group in which the high dose ESZ group had an incidence that was also at least twice that of the low ESZ dose and placebo groups (incidence in placebo, 1 mg ESZ and 2 mg ESZ groups, respectively, are shown):

- Headache (0%, 0%, 1.9%)
- Nausea (0%, 0%, 1.0%)
- Vomiting (0%, 0%, 1.0%)

Nervous system AEs met the above dose-dependent incidence criteria in the two 2-week elderly trials (trials 190-047 and 190-048, combined) with the incidence in placebo, 1 mg and 2 mg ESZ groups as follows: 1%, 1%, and 1.9%. Most of these events were dizziness, but also hypertonia and somnolence each occurred in one subject.

G. Specific Search Strategies on AEs Conducted by the Sponsor

1. AE Search Strategies Described in the ISS of the Submission. The ISS enumerates AEs of special interest among the clinical trials. These AEs, as follows, were chosen as common AEs for the drug class:

- Memory impairment: AE's described below.
- Convulsions: no reports of this AE.
- Drug dependence: no reports of this AE.
- Hallucinations: AE's described below
- Respiratory compromise: no reports.

Also refer to the next subsection H for the incidence of specific AEs (i.e. psychiatric-related AEs, neoplasia-related, and others) that were not a focus in the ISS but are areas of focus for this review.

Memory impairment AEs. This type of AE was reported in a total of 44 out of 1839 ESZ subjects and in only 1 placebo S in the clinical trials, combined. 2 of the ESZ subjects were ADOs (one S dropped out due to multiple AEs including memory impairment). Both of the subjects who were ADOs started having memory impairment within days of treatment, were non-elderly and did not have pre-existing conditions or any apparent risk factors for memory impairment. These two subjects continued to have memory impairment during most of the treatment period until study drug was discontinued. There were no SAEs due to memory impairment.

The largest incidence of memory impairment occurred in the study of patients with history of benzodiazepine abuse (study 190-016). Almost all of these subjects (26 out of 28 subjects) who were also primarily male subjects (22 out of the 26 total subjects were male) reported memory impairment in this 14-day, 6-way cross-over study. This AE was in only 1 S during placebo treatment and in 5 subjects during diazepam treatment compared to 13 subjects during ESZ treatment in this study. This study used 3 mg, 6 mg and 12 mg dose levels of ESZ. None of the subjects reported memory impairment after the 3 mg dose.

Subjects in daytime and other nighttime studies reported memory impairment at the 3 mg dose or at lower dose levels (as low as 1 mg). In the large long term study (190-049) of Chronic insomnia patients this AE was reported in 8 ESZ subjects during double-blind treatment (this study used the 3 mg dose, N=593, and a placebo group; N = 195). 4 subjects reported memory impairment during the 3 mg ESZ open-label phase (N= 471).

Memory Impairment in the Two 2-Week Elderly Trials (190-047 and 190-048)

Upon examination of the incidence of AE's described in study reports for each of the two 2-week elderly trials, the following results are noted. In the 2-week PSG study (190-047), none of the 128 placebo subjects reported memory impairment, while 2 out of 136 ESZ subjects (1.5%) reported memory impairment. Both ESZ subjects reporting memory impairment (477710 and 637701) complained of being "forgetful" after receiving approximately one week or two weeks of treatment, which lasted for approximately one day in each subject. Both subjects also complained of intermittent nervousness during treatment ("irritable/cranky" or "feeling restless").

In the 2-week subjective sleep study (190-048), only one in subject reported memory impairment. The subject was in the high dose ESZ group (2 mg/day, 79 subjects in this group) and experienced "forgetfulness" approximately 10 days after the onset of the 2-week double-blind treatment phase. This AE resolved within approximately one day after cessation of treatment (this healthy, 72-year-old female completed the trial as planned, and required no medication).

Two subjects in the 2 mg group (out of 79 subjects) had the AE of confusion. No SAE's of confusion were reported in any of the 80 placebo subjects in this group or in any of the 72 subjects in the 1 mg ESZ group. Both subjects were women (ages 69 and 74 years old) who began experiencing confusion within a day to a few days of treatment. In one of the subjects, confusion occurred on three occasions, each on three separate days, at 7:00 and resolving by 10:00 each day. The other subject experienced confusion only on a single day at 10:00 which resolved on the same day. Both subjects had unremarkable physical exams and past medical histories, and neither of them required treatment for their episodes of confusion.

One 2 mg ESZ treated subject had abnormal thinking as an AE that started within a few days of double-blind treatment and continued until the end of the study (it was reported as ongoing, on her last study visit). This subject was a healthy 76-year-old female. The event was considered mild and did not require medication and the subjects completed the study is planned.

Hallucinations.

A total of 15 ESZ subjects (out of 1839 ESZ subjects; 0.8%) and no placebo subjects reported hallucinations in the clinical trials, combined. The largest incidence of subjects reporting this AE in a given trial was in Study 190-016, the study of subjects with a history of benzodiazepine abuse that also had the largest incidence of subjects with memory impairment, as previously described. A total of 7 out of the 26 subjects had hallucinations after ESZ treatment (2 subjects

after 6 mg and 5 subjects after 12 mg). 2 of these subjects had additional episodes of hallucinations at the 12 mg ESZ dose-level or during treatment with 20 mg of diazepam.

There were no ADOs or SAEs due to hallucinations. The above AEs of hallucinations were generally brief episodes and occasionally intermittent episodes of primarily visual hallucinations that occurred as soon as 30 minutes to an hour after the first dose of ESZ or after weeks or longer of treatment. subjects were young or old, male or female and several had no previous history of pre-existing conditions. However, the largest proportion of subjects were in Study 190-016 involving subjects with a history of benzodiazepine abuse who underwent 14 days of treatment at dose levels above 3 mg of ESZ in a 6-way cross-over design.

Hallucinations in the Two 2-Week Elderly Trials (190-047 and 190-048).
Upon examination summary table of the incidence of AE's for Study 190-047 no AE's of hallucinations were reported. However, several other nervous system-related and psychiatric-related AEs were reported. The overall incidence for nervous system events in this trial was 8.6% in the placebo group and 15.4% in the ESZ group. The incidence by type of AE is provided in the following for AEs that showed an incidence in the ESZ group that was at least 1% and at least twice that of the placebo group:

- Anxiety: 0%, 2.2% in the placebo group and the ESZ group, respectively.
- Emotionally ability: 0%, 1.5%.
- Nervousness: 1.6%, 3.7%.

One ESZ subject reported agitation (no placebo subjects reported this AE).

Anxiety was only reported in one subject in Study 190-048 (1 out of 72 subjects in the 1 mg/day ESZ group). Depression was reported in one 2 mg ESZ treated subjects and in no other subjects in the trial. Hallucinations or other psychiatric-related events were not reported. However, abnormal dreams were reported in 2.8% and 1.3% of subjects in the low and high ESZ groups, respectively and in no placebo subjects.

2. AE Search Strategies Described in the 120-Day Safety Update Report.
The following describes additional analyses of selected AEs and their association with other events provided in the 120 Update Safety Report. Results of additional analyses of laboratory, vital sign and EKG data are also described in the Update Report and are described later in this review (subsection J-L). The sponsor had no ongoing studies, and therefore had no new safety information to provide. However, they provided results (primarily safety information) based on additional analyses conducted on the safety data from the clinical trials described in the original NDA submission. This review focuses on safety-related observations that may be considered interpretable results or were potentially salient findings.

a) Results of an Analysis on AE's of Infection. Because of higher rates of infection reported in ESZ subjects compared to placebo subjects in several clinical trials, the sponsor conducted additional analyses of infection AE's, based on a categorization of these AE's by the type of verbatim term. This reanalysis was conducted for Studies 190-046 and -049. As previously described, Study 190-046 (a 6-Week nonelderly Chronic Insomnia Trial) showed an incidence of infection (as a Preferred Term) of 3%, 4.8%, and 10.5% in the Placebo, 2 mg ESZ and 3 mg ESZ groups, respectively. Study 190-049 revealed in incidence of infection of 6.7% in the placebo group compared to 15.9% in the 3 mg ESZ group of the 6-month double-blind phase, as previously described.

The sponsor conducted their reanalysis by first examining the verbatim terms in these subjects (subjects with the AE of infection, as a Preferred Term). These subjects were categorized into the following subcategories based on the verbatim term that was used: cold symptoms, common cold, head/chest cold, upper respiratory infection, respiratory or chest infection, and other infection.

Before describing the results of the sponsor's reanalysis of data from subjects with the reported Preferred Term AE of infection, it is important to note one major caveat regarding the interpretation of the sponsor's results. The sponsor only conducted the analysis on subjects with the Preferred Term-AE of infection, which does not capture a number of other subjects that also had infection that was reported using a different Preferred Term (e.g. bronchitis, pharyngitis, rhinitis, urinary tract infection, flu syndrome, fever, vaginal moniliasis, and others). It is noted that some of these other events showed an incidence in treatment groups, suggestive of a drug-related effect and in some studies a dose-dependent effect (i.e. in a trial using multiple dose levels). Therefore, the ability to interpret the results of the sponsor's analysis is limited and the sponsor's results and any conclusions from these results can only be considered preliminary.

The following summarizes the results of the sponsor's reanalysis of Preferred Term infection AE's. The incidence of the subjects within each verbatim term category in Studies 190-046 and 190-049 was first determined by the sponsor. Based on the results, the sponsor concludes that the majority of subjects in either treatment group were in the first five categories (common cold/upper respiratory infection-related categories), as very few subjects were in the "other infection" category.

The sponsor also determined the incidence of subjects having both of the following AE's (as Preferred Terms): rash and infection. These results showed no evidence for a relationship between these two AEs. However, the sample size of subjects within several categories was small, such that this conclusion can only be considered preliminary. Also this analysis does not include subjects reported to have rash-related signs or symptoms (e.g. pruritus, erythema dermatitis, among others). Furthermore, the analyses does not capture all subjects who may have had infection, as other infection-related Preferred Terms were used on a number subjects (e.g. rhinitis, pharyngitis, and others), as already mentioned.

A further analysis of subjects within the verbatim-term AE category of "cold/upper respiratory infection" was conducted to determine the frequency of this type of an event in each subject. This category of verbatim term AEs was only reported once in a majority of the subjects with this type of AE. Treatment groups were also similar on the incidence of subjects completing the trial who were within this category of AEs.

The sponsor also determined the duration (in days) of infection in the subjects in the common cold/upper respiratory infection-related verbatim-term AE categories and both studies showed similar results as follows. The 3 mg ESZ subjects generally showed numerically greater mean days of infection, greater number of days at the 90th percentile, as well as a greater maximum number of days of infection, than the placebo subjects. In the longer study (Study 190-049), ESZ subjects had a mean duration of 18 days of infection compared to 8.5 days in the placebo subjects and a maximum number of days of 156 compared to 33 in the placebo subjects. Treatment groups were similar in median days of infection in both studies, suggesting that a prolongation of cold/upper respiratory type of infections may occur in a subgroup of patients treated with ESZ compared to placebo. The sponsor also examined the mean change from baseline on WBC count, % neutrophils and % lymphocytes in subjects with infection in each treatment group. However, in most cases sample sizes were small (in the placebo group), such

that results are difficult to interpret, in addition to the problem of the timing of blood sample collection to the time when peak effects associated with a given infection can be anticipated.

Other analyses were conducted that in the opinion of this reviewer, did not yield meaningful results primarily due to inadequate sample sizes. Furthermore, studies were not specifically designed for examining potential effects of the study drug on infection or related events. Therefore, other results provided in the 120-Day Report are not described in this review.

b) Results of an Analysis of the Incidence of Accidental Injury in Subjects With or Without a CNS AE. Because the incidence of subjects with the AE of accidental injury was greater in ESZ subjects compared to placebo subjects in four trials, the sponsor determined the incidence of these subjects who also had a CNS AE compared to those who did not have CNS AE, and the incidence of subjects with only a CNS AE without accidental injury. The incidence of accidental injury in treatment groups in each of the four Chronic Insomnia efficacy trials was as follows:

- Study 190-046 (the 6-week non-elderly adult trial):
  5.1% in placebo subjects, 6.7% in 3.0 mg ESZ subjects.
- Study 190-049(6-month double-blind phase in non-elderly adults):
  5.6% in placebo subjects, 7.3% in 3 mg ESZ subjects.
- Study 190-047 (2-week elderly trial):
  1.6% in placebo subjects, 2.9% in 2 mg ESZ subjects.
- Study 190-048 (2-week, elderly trial):
  0.0% in placebo subjects, 2.5% in 2 mg ESZ subjects.

Since, the sponsor's analysis on the incidence of accidental injury and CNS AEs is difficult to interpret for a number of reasons (e.g. insufficient cell size, the temporal relationship between CNS events and accidental injury and the type of CNS event were not considered, among other limitations). One finding that may be notable, is that the incidence of subjects with a CNS AE who also experienced accidental injury was generally numerically greater in the ESZ groups (particularly in the high dose group of each trial) compared to the placebo group in each trial (based on results in Table 9.3.6.2-1, on page 118 in the ISS.pdf file). Results on from the open-label phase of Study 190-049 are not described, since this phase of the trial was not placebo controlled and open-label. The following shows the incidence of subjects in the high dose group with CNS and accidental injury AEs compare to placebo in each trial:

- Study 190-046:
  0% in placebo subjects (0/5 total subjects with accidental injury),
  20% in 3 mg ESZ subjects (1/4 total subjects with accidental injury).
- Study-049 (double-blind phase):
  18.2% of placebo subjects (2/9 total subjects with accidental injury),
  30.2% of 3 mg ESZ subjects (13/30 total subjects with accidental injury).
- Elderly Studies 190-047 and 190-048 (pooled):
  0% of placebo subjects (0/2 total subjects with accident injury),
  17% of 2 mg ESZ subjects (1/5 total subjects with accidental injury).

However, most of these results can only be considered preliminary as the cell sizes were generally small.

H. Treatment Emergent AEs

It is important to note that the incidence of gender specific urogenital AEs did not appear to calculated properly in the summary tables in the ISS (such as summary Tables VIIIH1-10 in the appendix of this review, as provided by the sponsor) and in at least some of the study reports (this error was also revealed from a spot check of a summary table of AEs in the study report for Study 190-049). Rather than using the number of subjects within the appropriate gender group for the denominator when determining the incidence of a gender specific AE, the sponsor appeared to use the total sample size of males and females in the denominator. Since a number of ESZ subjects (contrasted to only a few placebo subjects) reported various urogenital AEs (e.g. breast tenderness, menstrual-related AEs, among others) the sponsor will need to recalculate the incidence of urogenital AE's using the correct denominator.

One of the most common and consistently drug-related and dose-dependent AE in each trials and in trials, combined, was unpleasant taste. This AE was generally reported in approximately 10 to over 30% or more ESZ subjects (dose-levels combined) compared to only a few placebo subjects (refer to Tables VIIIH1-10 in the appendix for values). At the recommended dose level of 3 mg, up to 34% of 3 mg ESZ treated subjects reported unpleasant taste. Unpleasant taste resulted in 10 ESZ subjects (given 3 mg/day) terminating treatment compared to only one placebo subject who stopped treatment due to this AE, during the 6-month double-blind phase of the longer term trial (Study 190-049). The incidence of this AE in individual efficacy trials was previously described under Section VI, as this AE is of particular interest regarding the integrity of the double blind study design of the sponsor's trials, as previously discussed. Conclusions and recommendations regarding this issue are addressed in the final section of this review.

The overall incidence of AEs generally showed the greatest numerical treatment group difference (between placebo and ESZ groups or treatment conditions) in the short-term daytime trials (Phase I trials). The greatest treatment group differences also appeared to be associated with trials using the highest daily dose-level (≥3.5 mg ESZ), which included daytime and night-time short-term Phase I trials. Results on specific AEs are described for each study-type category, below.

Search strategies for specific AEs of memory impairment, hallucinations and others, were conducted by the sponsor and described in the ISS. The incidence of these AEs was previously provided in Section G of this review and will not be a focus in sections below. However, additional search strategies for AEs of special interest that could not be found in the submission were conducted by the author of this review. The results of these search strategies of the use of special interest are described below. AEs considered to be of special interest are those that were either unexpected for the drug-class, or particularly serious in nature, and/or were prominent AEs (e.g. more common AEs that also show treatment group differences and are potentially serious in nature).

The Incidence of AEs in Daytime Short-term Trials (1-7 day long Phase I trials). Some of these trials generally used single dose levels of ESZ above 3.5 mg and the pooled data showed the following samples sizes for each treatment group or treatment condition (several trials used a cross-over design): placebo (N=124 subjects), 1 mg ESZ (N=24), 2 mg (N=52), 2.5 mg (N=6), 3 mg (N=135) and ≥ 3.5 mg (N=91). All ESZ treatment conditions/groups showed a greater incidence in overall AEs (by approximately 20-30% greater) for most groups than placebo. One

AE that did not appear to be prominent in other trials was "hiccup" occurring in 4-6% of subjects in the 2 highest dose groups compared to 0% in all lower dose groups and placebo.

CNS AE's were the most common AE's in these trials (an incidence of 24%, 56%, 62%, 69% in placebo, 2 mg, 3 mg, and ≥ 3.5 mg ESZ groups, respectively). Dizziness was common and most common in the 3 mg and above 3.5 mg groups (25% and 34%, respectively) compared to 17-19% in lower dose groups and 11% in placebo. Confusion occurred in 3% of subjects in each of the two highest dose-levels with 0 to less than 1% of subjects reporting confusion in lower-dose and it placebo groups. Similar incidence rates were observed with abnormal gait and "speech disorder" (each AE was in 3% of subjects in the highest dose level and 0 to <1% in all other groups). Refer to Table VIIIH1 for additional AEs that were generally not unexpected for this drug-class.

The incidence of psychiatric related AEs were greater with ESZ than with placebo treatment (including mood changes such as depression, emotional lability and euphoria, AEs of anxiety or nervousness and hallucinations which occurred in only 1 S at the ≥3.5 mg dose-level) as follows:

- Only 0.8% with placebo
- 6.1% at all ESZ dose-levels, combined
- 4.4% at the 3 mg dose-level (which is the recommended dose-level in proposed labeling).

Abnormal thinking was a common AE at the dose levels of 3.5 mg of ESZ and above (5.5%; 5/91 subjects) compared to 1.5% (2/135 subjects) in the 3 mg ESZ dose-level, and 1.6% of placebo subjects, as shown in Table VIIIH1.

Accidental injury occurred in 2.2% of subjects with the two high ESZ dose levels (3 mg and ≥ 3.5 mg dose levels), compared to 0% at the lower dose levels and with placebo (only 24 subjects were at the 1 mg dose level, such results in this group are not described here).

The Incidence of AEs in the Night-time Short-Term Trials (healthy volunteers, Cross-over Study 190-024 and Parallel Group Study 190-026, combined).

Table VIIIH2 in the appendix summarizes the results. Approximately 100 subjects were in the placebo, 2 mg, 3 mg and ≥3.5 mg ESZ treatment conditions/groups and approximately 50 subjects in a 1 mg ESZ group/condition in these two trials, combined. The results shown in the summary tables did not reveal any new or remarkable AEs showing treatment group differences than already were observed in the short-term daytime trials. One exception is that the overall incidence rates of AEs (total AEs) were generally lower in the night-time trials compared to the day-time trials at the same dose-level. This observation is not unexpected given that subjects in night-time studies receive ESZ at bedtime and are expected to be asleep by Tmax when most AEs are likely to occur.

Most Preferred Term AE's showed an incidence of < 2% in more commonly < 1% of subjects in each ESZ group. The following AE's are some notable exceptions. **Dizziness** occurred in up to 4% of subjects at the highest dose-level (≥ 3.5 mg) compared to 0 subjects with lower doses and with placebo. **Abnormal vision and diplopia** were each reported in 3% or 2% of subjects (respectively) at the highest dose level compared to few to no subjects at lower dose levels and in subjects with placebo treatment. **Nystagmus** was reported in a few subjects at high dose-levels.

Psychiatric-related AEs did not appear to be as prominent as observed in the night-time trials in this healthy volunteer population (occurred in approximately 3% of subjects at the 3 mg dose-level compared to 1.8% of placebo subjects and 0.9% at lower ESZ dose-levels).

Digestive system AE's were also common and appear to be drug-related compared to placebo treatment as shown in Table VIIIH2. These AE's included dry mouth, anorexia, constipation, diarrhea and abnormal stools.

Unpleasant taste was reported in 34 to 46% of subjects at all ESZ dose-levels except for the lowest dose level of 1 mg (4.2% of subjects), while unpleasant taste was reported in 8.9% (11/124) subjects treated with placebo.

The Incidence of AEs in the Night-time Short-Term Trials in Patients with Chronic Insomnia (Studies 190-025 and 190-045, combined).
These two trials, combined had approximately 60 to 70 subjects in each group/condition (primarily single dose trials) as follows: placebo, 1 mg, 2 mg, 2.5 mg and 3 mg dose-levels. The overall sample size for all ESZ subjects, combined, was a total of 77 subjects, as the trials were cross-over studies.

The results in Table VIIIH3 in the appendix fail to reveal any remarkable or new findings not observed in other short-term trials. Not surprisingly, the overall incidence rates of AEs (total AEs) and AEs that appeared to be dose related were greater in this patient population than in the healthy volunteer population in short-term night-time trials.

An AE not previously reported in the other short-term trials was **migraine**, which occurred in 2 ESZ subjects.

Some gastrointestinal AEs, such as diarrhea, dyspepsia and nausea appeared to be more marked (more common in ESZ subjects, as well as occurring with twice the incidence compared to placebo subjects). These AEs occurred in 6.5%, 4% and 9% (for each AE, respectively) in all ESZ subjects (at all dose-levels, combined) compared to approximately 1 % of subjects with placebo treatment for each of these AEs (except for nausea; 4% with placebo compared to 9% with ESZ treatment). **Dry mouth** was also more prominent among subjects within this study-type category showing an incidence of approximately 3% at the 2.5 mg and 3 mg dose-levels compared to about 1% with placebo treatment.

Psychiatric related AEs occurred in 4% of the 3 mg ESZ treated subjects compared to no subjects with placebo treatment.

The Incidence of AEs in the Night-time 2-Week Trials in Elderly Patients with Chronic Insomnia (Studies 190-047 and 190-048, combined). These two trials employed a parallel group design with the following treatment groups: placebo (N=208), 1 mg ESZ group (N=100), and a 2 mg group (N=215). Table VIIIH4 summarizes the results of AEs that showed an incidence of at least 2% in ESZ treated subjects and was greater than the incidence in placebo subjects. As expected some AEs appeared to be more prominent in this elderly insomnia patient population contrasted to results from the trials of non-elderly patient populations, noting that the highest dose employed in the elderly 2-week trials was only 2 mg (compared to the 3 mg and higher dose-levels in other trials). The AEs that show treatment group differences in Table VIIIH4, are generally similar to the AEs observed in the other trials.

Several AEs involving pain that were not generally observed in the short-term trials showed treatment group differences in these 2-week elderly trials: pain, back pain and chest pain had an incidence of 2-4% in at least the2 mg ESZ group compared to 0-1.9% in the placebo group).

Dry mouth was a more common AE at the 2 mg dose-level (7%), than observed in non-elderly trials, and occurred with twice the incidence in this ESZ group compared to the placebo group.

CNS AE's included AEs of ataxia, stupor or confusion that were reported among 4 ESZ subjects (not shown in the summary table).

Hypothyroidism was only reported in one 2 mg ESZ S, which was not observed in the shorter-term non-elderly adult trials.

Accidental injury was reported in 3% of subjects in the 2 mg ESZ group compared to 1% of subjects in the placebo group and 0% of subjects in the 1 mg ESZ group.

Psychiatric-related disorders were common in these 2 elderly 2-week trials showing an incidence of 5 to 6% even at these lower dose levels of 1mg and 2 mg ESZ groups compared to 1.4% of placebo subjects. These AEs were previously described in greater detail in the section on AEs of special interest.

Refer to Table VIIIH4 for additional AEs showing treatment group differences that were generally, also observed in previously described trials.

Since the sponsor's summary tables in the ISS only showed AEs of at least 2% in ESZ subjects for the studies combined, the following paragraphs describe AEs observed in each individual trial that revealed an incidence of at least 1% in ESZ subjects and was at least twice that of placebo.

AEs in Study 190-047. When examining the summary table on the incidence of AE's for Study 190-047 (the 2-week PSG elderly trial) the following AEs showed an incidence of at least 1% in the ESZ group and was also at least twice the incidence of the given AE in the placebo group (see under the previous section and an east of special interest regarding nervous system related AEs, except for dizziness, which is provided below):

- Peripheral edema (0%, 2.2% in the placebo group and ESZ group, respectively).
- Arthralgia (0.8%, 2.2%).
- Dizziness (1.6%, 6.6%).
- Dry mouth (1.6%, 8.8%).
- Thirst (0.8%, 1.5%).
- Accidental injury (1.6%, 2.9%).
- Back pain (0%, 2.2%).
- Pain (3.1%, 5.9%).

A common AE of unpleasant taste in ESZ subjects but not in placebo subjects was observed in almost all of the trials described in this review and as discussed elsewhere in the review.

Results on AEs in Study 190-048 (the other 2-week elderly trial, a subjective sleep study) are described here. The following are AEs is that occurred in at least 1% of subjects in either of the ESZ group (one and 2 mg groups, n=72 subjects, n= 79 subjects in each group, respectively) and showed an incidence that was at least twice that observed in placebo (the incidence in the placebo, 1 mg ESZ, and 2 mg ESZ groups, respectively, is provided):

- Abnormal dreams (0%, 2.8%, 1.3%).
- Dizziness (3.8%, 1.4%, 3.8%).
- Accidental Injury (0%, 0%, 3%).

- Neuralgia (0%, 2.8%, 0%).
- Paresthesia (0%, 0%, 1.3%).
- Vertigo (0%, 1.4%, 1.3%).
- Dyspnea (1.3%, 0%, 2.5%).
- Pruritis (0%, 4.2%, 1.3%).
- Dry eyes (0%, 0%, 1.3%).
- Urinary incontinence (0%, 0%, 2.5%).
- Urinary tract infection (1.3%, 2.8%, 0%).

The above does not included memory impairment, psychiatric-related or other neurological events previously described under the section on AEs of special interest. As in other trials unpleasant taste was a common AE in the ESZ groups and is described in more detail elsewhere in this review.

One subject in the 2 mg ESZ group had an event of **hypothyroidism**, but this subject had a history of hypothyroidism upon entry into the study.

The Incidence of AEs in the 6-Week Trial in Non-Elderly Patients with Chronic Insomnia (190-046). Table VIIIH5 in the appendix generally shows no new or unexpected AEs, than already observed in previously described trials with some exceptions in which some AEs appeared to be more common than observed in previous trials, or were AE's that were generally not observed in previous trials, as follows. Some of the information below was taken from end-of-text summary tables showing the incidence of all AE's (as Table VIIIH5 only shows the incidence of AE's occurring in at least 2% of ESZ subjects that were greater in the subjects than placebo subjects). It is important to note that potentially related AEs, when combined may be more common and may not appear in the in the sponsor's in-text summary table (Table VIIIH5) which is the reason for describing observations below on the basis of these end-of-text table and providing these more complete tables in the appendix (this was also provided for other efficacy trials below).

Infection and skin/appendage system AEs of primarily rash and pruritus were not as prominent in previously described trials, but were common in ESZ subjects (i.e. ≥5% incidence) in this longer term, six-week trial, and occurred with twice the incidence in ESZ subjects compared to placebo subjects. The skin/appendage system AEs showed an incidence of 2%, 9% and 8% in placebo, 2mg and 3 mg groups and represent primarily AEs of rash and pruritis. Infection which is not an expected AE for the drug-class, showed an incidence of 11.5% in the 3 mg ESZ group, 4.8% 2 mg ESZ group and only 3% in the placebo group. Viral infection showed an incidence of 3% in each ESZ group compared to only 1% in the placebo group.

Migraine was reported in 1.9% of 3 mg subjects, 1% of 2 mg subjects and no placebo subjects.

Dry mouth and dizziness showed treatment group differences, similar to that observed in previous studies. The incidence of each of these AEs increased numerically with increasing dose (each AE occurred in 7% of subjects in the high dose group, 5% in the low dose group and 3 or 4% of placebo subjects).

Ulcerative stomatitis and thirst were generally not observed in previously described shorter-term trials but were reported in a few ESZ subjects in this 6-week trial. This AE is noted since additional ESZ subjects had similar AEs in the longterm trial during the 6-month double-blind treatment phase (Study 190-049) which is described later. These AEs could be reflecting clinical features of dry mouth associated with long term treatment. Ulcerative lesions can be

considered severe AE's in that they are not only painful, but can ultimately lead to infection or other complications, particularly in higher risk populations (i.e. patients at risk for infection, among others).

Psychiatric AEs may not be unexpected for the drug-class but are described in the following because of their common occurrence in the ESZ groups at the therapeutic dose-level being proposed by the sponsor for labeling and due to the potentially serious nature of these events. The incidence of psychiatric-related AEs in this 6-week trial of non-elderly insomnia patients was 6 or 10% of subjects in the ESZ groups compared to 3% of placebo subjects. These AEs included agitation in 1 S in each of the two ESZ groups (and no placebo subjects), hallucinations in 3%, 2% of subjects in the 3 mg and 2mg groups and no placebo subjects, depression, anxiety, nervousness and emotional lability.

Additional central nervous system-related events that are not unexpected for the drug-class but are serious in nature were the following. **Abnormal thinking** which was not counted among psychiatric related AEs, above, was reported in a 3mg ESZ S. **Confusion** was reported in 3% of subjects in the 3 mg group compared to no subjects in the low-dose and placebo groups. **Stupor and abnormal gait** were each reported in one S in the high-dose group.

Hepatitis and melena were each reported in one S in the high-dose group and not in other groups and are noted due the serious nature of these events.

Due to some preclinical data showing reproductive hormonal changes in animal studies (per multiple communications with Dr. Aisar Atkrachi, Pharmacology/Toxicology reviewer) and preclinical reports of mammary gland neoplasia, the following **genitourinary (GU) AEs** are noted and of which none were observed in any of the placebo subjects:

- Amenorrhea in 1, 3mg ESZ S
- Dysmennorhea in 2, 2mg ESZ subjects
- Fibrocystic breast in 1, 2 mg ESZ S
- Gynecomastia in 1, 2mg ESZ S

The Incidence of AEs in the Longterm Trial (190-049).

Refer to Tables VIIIH6-10 for a summary of the incidence of AEs for the 6-momth double-blind phase and the open label phase of Study 190-049. The first set of these summary tables only show AEs with at least a 2% incidence in ESZ subjects that is also greater than placebo. The last set of these tables were found as end-of-text tables of the study report and are of all reported AEs independent of the incidence reported. These tables are shown since a number of AEs that are clinically related and should be considered when combined, such that these related AEs may fail to appear in the first set of tables but when combined could be common AEs in ESZ subjects compared to placebo subjects. In addition to results for open label treated subjects considered as a single group in Tables VIII-7 and -9, these tables as provided by the sponsor also show the incidence of open-label AEs in each of the two subsets of open-label subjects when subgrouped by previous double-blind treatment exposure (the subset previously assigned to double-blind ESZ and the other subset previously assigned to double-blind placebo). It is important to note the limitations in comparing data from these subgroups, given that the open-label phase is not designed for making such comparisons for determining differences with 6 month versus 12 months of treatment with the study drug on safety.

Results of the Double-blind Phase of Study 190-049. The double-blind phase study revealed treatment group differences between placebo (N = 195) and 3 mg ESZ (N = 593) of AEs that were similar to those in the shorter-term trials. These AE's included **dry mouth,**

dizziness with a small trend for a numerically greater incidence for abnormal vision (but incidence is <2%), and **neurological system AEs** that are generally not unexpected for the drug-class. The following paragraphs describe AEs of special interest. These AE's appeared to show treatment group differences (using the twice greater than placebo group criteria) and were unexpected AE's for the drug class. Some of these AE's were also common (i.e.>5%) in ESZ subjects or were serious in nature. These AE's were primarily found in End-of-Text tables of the study report. Additional information on AE's of special interest was found in a Safety Update submission that is described separately, below.

As previously described, the incidence of gender specific AE's using the gender appropriate number of subjects in the denominator cannot be found in the end of text tables or summary tables that were examined (i.e. in the ISS or the study report for this trial).

Neoplasia AEs. While no placebo subjects (out of 195 subjects) had AEs of this type (with the AE term of neoplasm, neoplasia, or cancer), several ESZ subjects had this type of AE as follows (the 3 mg ESZ group, N= 593):

- Body as a Whole: neoplasm in 5 subjects (0.8%); type of neoplasia was not specified or could not be found.
- Breast Neoplasia in 2 subjects[10] (?%, could not find the incidence for women only)
- Prostate neoplasia in 1 S (?%, could not find the incidence for men only)
- Hepatic neoplasia in 1 S (0.2%)
- Mouth neoplasia in 1 S (0.2%)
- Skin benign neoplasm in 2 subjects (0.3%)
- Skin carcinoma in 3 subjects (0.5%)
- Additional AEs of neoplasia reported in the Open-Label Phase are described in the subsection on the Open Label phase, below (reported in a total of 7 Subjects in the Open-Label Phase)

The above reflects AEs up to 14 days after treatment (as described in the data source table: Table 8.1 starting on p.478 of the ISS.pdf file).

It is not clear why the above AE's were not reported as serious events. AE's of neoplasia that resulted in adverse dropouts were previously described subsection F on dropouts due to AE's which included in each of the following: the hepatic neoplasia (multiple tumors found in the breasts, lung, kidney and liver revealed by CT), breast neoplasm, neoplasm (" nodule in throat" in a 62-year-old). It is not clear if these adverse dropouts were also counted among the above AE's or if they reflect additional AE's of neoplasia. Another adverse dropout of subject reported as having "thyroid disorder" it was described as having a "nodule on the low side of the thyroid" is also previously described. It is not clear why these events, particularly events reported as neoplasm or not classified as SAE's. Furthermore, a discussion on neoplasia could not be found in the ISS or in the study report for this study, despite the preclinical concerns of neoplasia

1. [10] The incidence of these AEs using the number of subjects for the appropriate gender could not be found in the ISS or in the study report for 190-049 (a summary table did specify values were those the given gender yet, this review conducted a spot check for a gender specific AE that did appear to reflect the incidence for the total number of female and male subjects, combined). For example refer to the table on page 78 of the 190-046.pdf showing that 2 or 1.9% of subjects had dysmenorrhea, yet if calculated using 66 women as the denominator one obtains the value of 3%.

expressed by the Division in previous meetings with the sponsor, as well as similar concerns expressed for zopiclone under the zopiclone IND that was ultimately withdrawn (see Section IC of this review for details).

A number of AE's of neoplasia were reported in the trial, despite unusual and rather **stringent entry criteria for screening subjects at risk for neoplasia or with a history suggestive of neoplasia** that were employed in this trial, as follows (also described in Section VI):

- Women at risk of breast cancer must have a documented negative mammogram within 12 months of study entry
- subjects at risk for lung cancer must have a documented negative chest s-ray within 12 months of the study
- Exclusion criteria #2: subjects with a "history of, or current malignancy except for non-melanomatous skin cancer" were to be excluded
- All subjects with active thyroid disease must also have a negative thyroid scan within 12 months of the study.

These exclusion criteria are generally atypical for Phase III trials and large, longer-term studies intended to establish adequate longterm safety, and 3 of the above criteria with were not listed in the eligibility criteria in the study report, but rather were found in this section describing procedures during the baseline for screening visit of the study.

Note that 3 ESZ subjects had skin neoplasia (or skin carcinoma) AEs and 2 subjects had benign skin neoplasia AEs, as above. A long-term rodent cancer study was reported to show skin neoplasia in animals housed together that had multiple trauma-induce skin lesions (animals reportedly fought) but skin neoplasia did not occur in another long-term rodent study in which animals were individually housed (according to the Pharmacology, Toxicology reviewer, Dr. Aisar Atrakchi, as communicated to the author of this review on multiple occasions including on 5/7/03).

Given the preclinical and clinical observations of skin neoplasia, as above, the following **skin-related AEs** are noted. The total incidence of skin and appendages AEs in Study 190-049 was 9.2% in placebo subjects and 12.1% in ESZ subjects of which the majority of these AEs were **contact dermatitis and rash**. Similar skin AEs were previously described in this review and occurred in 8 to 9% of ESZ subjects compared to 2% of placebo subjects in the 6-week trial.

Six ESZ subjects had GU-related neoplasia, as above. Refer to the next paragraph for other GU-related AEs.

Genitourinary AEs. Few placebo subjects had GU system AEs (dysmennorhea in 4 subjects, menorrhagia, metrorrhagia and endometrial disorder, each in 1S out of 195 subjects) compared to the following incidence of ESZ subjects (out of 593 subjects) reporting breast-related or uterine/vaginal or menstrual-related AEs:

Breast-related-AEs

- Breast pain in 9 S
- Breast engorgement in 1 S
- Breast enlargement in 1 S
- Fibrocystic breast in 1 S
- Mastitis in 1 S
- As above, breast neoplasm in 2 subjects
- Lactation in 1 S

Uterine/vaginal/menstrual-related AEs-

- Dysmennorhea in 16 subjects
- Menorrhagia in 3 subjects
- Metrorrhagia in 2 subjects
- Uterine hemorrhage in 1 S
- Vaginal hemorrhage in 3 subjects

The incidence of ESZ subjects reporting the following additional G-U AEs are noted, since they may be reflecting infection or are potentially serious events (only 1 placebo S reported vaginal moniliasis, among these AEs):

- Vaginal moniliasis in 9 subjects
- Vaginits in 4 subjects
- Cystitis in 3 subjects
- Pyelonephritis in 1 S
- Hematuria in 6 subjects

Double-blind and Open Label Phase of Study 190-049 on Selected GU or Reproductive Hormonal Related AEs Based on Results in the Safety Update Report. In the safety update report the sponsor determined the incidence of AEs in women that may be considered as related to reproductive hormonal/endocrine function (combined AEs that were breast-related, uterine-, vaginal- and menstrual-related AEs, vasodilation, and in 1 ESZ; hirsuitism) and revealed the following overall incidence during the 6-month double-blind phase of the study: 4.8% in the placebo group and 11.5% in the ESZ group. The majority of these AEs were breast-related or menstrual related.

In the Open Label phase of the study the overall incidence of reproductive hormonal/endocrine function AE's was 2.7% among open-label subjects who were previously assigned to double-blind placebo and 11.3% of open-label subjects, previously assigned to double-blind ESZ.

Comparing the Double-blind phase to the Open Label phase on the incidence of these AEs reveals a greater incidence in fibrocystic breast disease (0% of placebo and 0.3% of ESZ subjects in the double-blind phase compared to 2.3% of open-label subjects who previously received double-blind ESZ, and 0% of open label subjects who previously received double-blind placebo). These results suggest a potential effect of ESZ treatment over time on development of fibrocystic breast disease. Furthermore, breast neoplasia was not reported in any subjects in the open label phase. Breast neoplasia was reported in one subject in the open label phase of the trial, although, this subject received placebo treatment during the double-blind phase of the trial.

Respiratory and Infection-Related AEs. As shown in the AE summary tables, an unexpected observation was that the ESZ group showed a greater incidence of infection compared to placebo (6.7% placebo and 15.9% of ESZ subjects). Viral infection was reported in only 1.5% of placebo subjects and 2% of ESZ subjects. Note that some previously described GU AEs may be associated with infection or were recorded as a type of infection under GU system AE's. Other AE's such as conjunctivitis, some of the skin related AE's (dermatitis, fungal dermatitis, pruritis, among others), fever, flu syndrome, viral infection, ulcerative stomatitis, lymphadenopathy, and others observed in ESZ subjects, could be reflecting an infectious process (referred to summary

tables in the appendix). The following respiratory AEs may also be reflecting an inflammatory process and showed greater incidence of ESZ subjects reporting these events compared to placebo subjects, as follows (the incidence of ESZ and placebo groups, respectively):

- Bronchitis (0.5%, 1.9%)
- Pharyngitis (5.1%, 9.9%)
- Rhinitis (4.6%, 7.1%)

Psychiatric-related AEs. Hallucination AEs were previously covered in the section of specific search strategies. The incidence of AEs that were psychiatric-related in each group was 7.2% in placebo subjects and 14.8% in ESZ subjects. These AEs include the following: hostility (in 2 ESZ subjects and no placebo subjects), agitation (in 4 ESZ subjects and no placebo subjects), hallucinations (in 1 ESZ and no placebo subjects), anxiety, depression (4.6% of ESZ subjects, 1.5% in placebo), emotional lability, nervousness, neurosis and apathy. When including abnormal thinking with psychiatric-related AEs, then the overall incidence of psychiatric-related AEs is unchanged in placebo subjects (7.2%) but becomes 16.5% in the ESZ group.

Other AEs. A numerical trend for accidental injury in ESZ subjects compared to placebo subjects is noted (7.3% and 5.6%, respectively), while noting that central nervous system effects of sedative hypnotic agents may increase risk for accidental injuries and falls.

AE's of Pain. The ESZ group showed greater incidence in various types of pain than placebo subjects as follows:

- Pain (6.2% placebo subjects, 11.3% in ESZ subjects)
- Back pain (3.1%, 7.6%)
- Abdominal pain (5.6% and8.1%)

Hemorrhagic/blood coagulation-related events included previously described AEs (above). Rectal hemorrhage and melena were each reported in an ESZ subject and in no placebo subjects. Ecchymosis occurred in no placebo subjects and 1.9% of ESZ subjects.

Hepatomegaly and liver damage were each reported in one ESZ S and no placebo subjects. It is not clear to this reviewer why this ADO of liver damage was not classified as an SAE.

Mouth Lesions. This paragraph describes AEs involving lesions of the mouth because these events appear to be unusual in nature, yet are observations that were also revealed in the only other trial that was over a month long (the 6-week trial, 190-046) in non-elderly insomnia patients. Furthermore, neoplasia of the mouth was reported as an AE in 1 ESZ S and as an AE resulting in study withdrawal (neoplasm of "nodule in throat") in a 62-year-old subject in Study 190-049. The following AE's were reported in the double-blind phase of Study 190-049: ulcerative stomatitis in 3 ESZ subjects, mouth ulcer in 1 ESZ S and stomatitis in 1 ESZ compared to none of these AEs in the placebo subjects. Perhaps related to these AEs is dry mouth, which had a greater numerical incidence in ESZ subjects compared to placebo subjects, as in previous trials and was a common event in the ESZ subjects of this longer term trial (6.6% of ESZ subjects and 1.5% of Placebo subjects). Other previously described AEs that involved the oral/nasal mucosa or the airway were common AEs in the ESZ subjects with an incidence in ESZ subjects of approximately twice or greater than the incidence in placebo subjects. These AEs were the following events: rhinitis, pharyngitis and bronchitis.

Endocrine System AEs. The following endocrine-related AEs were reported in only ESZ subjects and not in placebo subjects unless otherwise specified: goiter in 3 ESZ subjects,

hypothyroidism in 3 ESZ subjects (1 placebo S) and parathyroid disorder in 1 ESZ S. Note that these AE's do not capture all potentially endocrine-related AE's, such as GU related AEs and others, previously described above.

Results of the Open-label 6-month Extension Phase of Study 190-049. Table VIIIH7 and VIIIH9 in the appendix shows the incidence of AEs during this phase of the study. This table also shows the incidence of AE's in the open label subjects, categorized according to their previously assigned study drug during the double-blind treatment phase of the trial (subjects who previously received placebo versus subjects who previously received ESZ during the double-blind phase). It is important to note that open label subjects, who were previously assigned to the double-blind ESZ group, are likely to represent a subgroup of patients with a favorable tolerability and greater efficacy with ESZ treatment compared to ESZ treated subjects of the double-blind phase who did not enter the open label phase of the trial. Consistent with this possibility many AEs showing treatment group differences during the double-blind phase (for the entire study population) generally showed a lower incidence during the open label phase than was observed in the ESZ group in the double blind phase. Similarly, many of these AEs also failed to show greater incidence rates during open-label phase compared to the placebo subjects in the double-blind phase (as shown by comparing the incidence under the "Open-Label" column in Table VIIIH7 or Table VIII9 to the incidence of the placebo subjects in the Double-blind phase in Table VIIIH6 or -8). These AEs included psychiatric-related AEs, dry mouth, infection and other AEs.

AEs are of special interest, reported during the open label phase are noted in the following.

Neoplasia. As above, none of the placebo subjects reported AEs of "neoplasia" or "neoplasm" during the double-blind phase of the study. A total of 7 subjects reported neoplasm in the Open-Label phase of the study (6 –months of open-label 3 mg/day ESZ; N=471 in the ITT Safety Population):

- Suspicious Papinicolau smear in 1 subject (0.2%): not listed as neoplasia but considered by this reviewer as neoplasia due to lack of information.
- Cervix neoplasm in 1 subject (0.2%).
- Skin benign neoplasm in 2 subjects (0.4%).
- Breast neoplasm in 1 subject (0.2%).
- Bladder neoplasm in 2 subjects (0.4%).

Six out of the above seven subjects with AEs were listed in the sponsor's summary table as previously being assigned to the 3 mg ESZ group of the double-blind phase (the subject with breast neoplasia had placebo in the double-blind phase). It is not clear to this reviewer why the above events of neoplasia or suspicious Papanicolaou smear were not categorized as SAE's. The above results are from Table 14.3.1.1B (starting on page 1200 of the190-049.pdf file).

Urogenital System AEs. The incidence of selected GU AEs and Reproductive Hormonal related AEs in women subjects in the double-blind and open label phases of the study were previously described based on an analysis of AE data described in the safety update report. Note that in Table VIIIH9 several UG system AEs (e.g. menstrual-related disturbances, breast-related events of pain, fibrocystic breast, enlarged uterine fibroids and others) continue to show at least greater number of the open-label ESZ treated subjects compared to the number of placebo treated subgroup during the double-blind phase in Table VIIIH8. Some of these AEs include those of neoplasia (as previously described). The following AEs are noted:

- Breast-related AEs (1 S with breast neoplasm, as previously noted): breast pain (5 subjects), fibrocystic breast (5 subjects). All of these subjects had previously been in the ESZ group in the double-blind phase.
- Menstrual or potentially related AEs were: metrorrhagia (5 subjects), dysmennorhea (7 subjects), amenorrhea (1S), hypomenorrhea (1S), and uterine hemorrhage (1S). All subjects were previously assigned to ESZ in the double-blind phase except for the 1 S with amenorrhea and the 1 S with hypomenorrhea.
- Vaginal infections or potentially related AEs included: vaginal moniliasis (11 subjects) and vaginitis (4 subjects).
- Uterine AEs: enlarged uterine fibroids (3 subjects), uterine hemorrhage, as above (1 S).
- UG bladder or renal infections or potentially related conditions included (bladder neoplasm in 1 S, as previously described): urinary tract infection (21 subjects), cystitis (2 subjects), urinary frequency (2 subjects), urinary tract disorder (in 2 subjects), hematuria (8 subjects), kidney pain (1 S), kidney calculus (1 S), urine abnormality (1 S).
- Suspicious pap smear, cervix neoplasm and other neoplasm AEs were previously described.

A comparison between the incidence of selected GU related AEs in the open-label phase compared to the double-phase of the study were previously described.

Other AEs. Table VIIIH9 shows that the incidence of **infection-related AE's (infection, infection-type specified, flu syndrome, viral infection, pain-related AE's (backpain, chest pain, abdominal pain)** among others show an incidence in the open-label phase of at least twice the incidence of the placebo treated subgroup in the previous double-blind phase of the study. **Pharyngitis, cough, sinusitis** are some additional AEs showing a similar pattern or a greater incidence during the open-label phase compared to the placebo treated subgroup in the double-blind phase. The following infection-related AE's showed an incidence in the subgroup of open-label subjects that were previously assigned to ESZ during the double-blind treatment phase that was at least twice the incidence in the subgroup of open-label subjects were previously assigned to double-blind placebo (the incidence in each subgroup, respectively, it is provided): viral infection (4.9%, 0.9%), pharyngitis (6.7%, 2.7%), and flu syndrome (8.1%, 3.6%). Other less common AE's also showed a similar pattern between these subgroups (as shown in Table VIIIH9).

Sections above do not focus on unpleasant taste, since this AE is described in previous sections regarding efficacy (in Section VI).

Dose-Related AEs

Tables VIIIH5 and -10 in the appendix shows the incidence of common AE's by treatment groups in studies 190-046 and 190-048, respectively (as provided by the sponsor). These tables only show the results of common AE's (incidence of $\geqslant$ 2%) in at least one ESZ group, and showed a lower incidence in the placebo group. These two studies were selected by the sponsor for describing dose-related AE's because they were studies conducted on patients with chronic insomnia, "in a setting that is representative of how eszopiclone will be used in patients." This reviewer also notes that these two trials had a fairly large sample size and employed a parallel group design, while other studies did not employ a multiple dose levels using a parallel group

design, or had smaller sample sizes. Study 190-026 was a fairly large trial using a parallel group design with multiple dose levels was conducted on healthy subjects.

Dose-Related AE's in Study 190-046. In summary, the six-week study in nonelderly adult patients with Chronic Insomnia revealed the following AE's as showing a pattern in the incidence of AE's of placebo< 2 mg ESZ< 3 mg ESZ (as shown in Table VIIIH5):

- Infection
- Dry mouth .
- Dizziness
- Hallucinations
- Unpleasant taste: this AE was the most common among these dose-dependent AE's with an incidence of 34% in the 3 mg ESZ group, which is the proposed recommended dose.

The following AE's showed an incidence that was similar between the placebo and low dose level of ESZ (2 mg) but numerically greater in the high dose group (3 mg):

- Dyspepsia
- Confusion

Dose-Related AE's in Study 190-048. As shown in Table VIIIH10 (in the appendix), the two-week study conducted in elderly Chronic Insomnia patients showed numerically increasing incidence of unpleasant taste with increasing dose level (as described in previous sections). The following AE's showed an incidence that was similar between the placebo and low dose level of ESZ but numerically greater in the high dose group (2 mg):

- Photosensitivity reaction
- Flatulence
- Confusion
- Dyspnea
- Urinary incontinence

Dose-Related GU System AE's in Studies 190-046 and 190-048. Since the incidence of gender specific AE's could not be found in the number of sections of the submission in which the values were calculated using the number of subjects within the appropriate gender for the denominator, it is not clear if the above tables were generated without using the proper calculation for gender specific AE's. Therefore, the sponsor needs to provide this information using the number of subjects for that specific gender in the denominator when calculating the incidence.

Subgroup Analyses of the Incidence of AE's on the Basis of Gender, Age-group or Race. Results of subgroup analyses on the incidence of AE's (on the basis of age, gender, or ethnicity) could only be found ISS for 2-and 6-week trials (data pooled) and for the double-blind phase of Study 190-049 in the ISS. Furthermore, only results of AE's that showed a difference in the treatment effects between the subgroups of > 5% were shown in the summary tables. Due to insufficient sample sizes for some of the sponsor's ethnic categories (sample sizes were <10 subjects in some categories), data from only the larger ethnic subgroups were analyzed. Table VIIIH11 summarizes the results (as provided in the ISS) for subgroup analyses showing treatment group differences of over 5%.

Only the results of subgroup analyses of ethnic subgroups are shown for the double-blind phase of Study 190-049, in Table VIIIH12. Gender subgroups in the double-blind phase of

Study 190-049 failed to show a difference in the treatment effect between males and females of > 5% on any type of AE (by Preferred Term). The sponsor only considered the age groups of < 65 and ≥65 -year-old subjects in their analyses. Yet, only two subjects were in the older group in Study 190-049, such that a subgroup analysis on the basis of age was not conducted.

I. Withdrawal Phase Adverse Events

1. Withdrawal Phase Adverse Events Described in the ISS

Integrated safety results on this topic could not be found in the submission. Although, several trials were not similar enough in study design to allow for pooling of data.

The incidence of withdrawal AEs were described in the ISS for two trials, separately. One trial was a nonelderly Chronic Insomnia 6-week trial (study 190-046) that had a single-blind placebo withdrawal phase after the double-blind treatment phase. The other trial was the 2-week Chronic Insomnia elderly trial (Study 190-047). It is not clear to this reviewer why only these two trials were selected. The results of withdrawal AE's from these trials were previously described (under Sections VIC and VID).

2. Withdrawal Phase Adverse Events Described in the 120-Day Update Report.

The safety update report describes the incidence of withdrawal AE's reported in the double-blind and open-label phases of the long-term Chronic Insomnia trial (Study 190-049). This trial did not include a single-blind placebo, discontinuation phase and the AE's described, were those reported within two weeks after treatment cessation. Given the known pharmacokinetic properties of the study drug, most withdrawal AE's would be anticipated to be most prominent with then the first few days after treatment cessation. Therefore, the results of these analyses are difficult to interpret. Yet, despite the limitations in the interpretation of the results, a greater incidence of nervous system AE's were reported in the 3 mg ESZ group (4.3%) compared to the placebo group (1.2%) during the double-blind, days of the trial. The following Nervous System AE categories showed a numerically greater incidence in the ESZ group compared to placebo (the incidence in each group, respectively, is shown):

- Depression (3%, 0%)
- Dizziness (0.9%, 0%)
- Anxiety, paresthesia, and decreased libido each occurred in 1 ESZ subject and in no placebo subjects.

J. Results on Laboratory Parameters (Hematology and Chemistry Parameters)

As previously described under subsection A the safety results from studies that were similar in study design were integrated. The integrated results for each study-type category are described below for results that included on-treatment values.

It is important to note that pooled safety data (for laboratory and other parameters) sometimes included data collected several days or more often 5-7 days after treatment endpoint. Since the study drug has a very short half-life and Tmax value, it is difficult to interpret results of values of most clinical data collected at time-points beyond cessation of treatment or results of pooled data that includes time points after treatment cessation. Table VIIIJ.1 in the appendix shows the time-point used in pooled studies within each study category (as provided by the sponsor in a 3/24/02 amendment submission during the pre-filing stage).

Outlier criteria and the incidence of outliers meeting pre-defined criteria were not provided in many studies or pooled studies, with some exceptions, noted below. Instead, shift

tables were provided (the incidence of subjects who shifted from normal at baseline to abnormal some time-point after randomization to this study drug). Results on some laboratory parameters for some studies were not provided in the ISS, either because the parameter was not obtained (such as hematocrit in some studies) or for other reasons (refer to section 8./10.H.6.7 in the ISS for details).

Outlier criteria were used in the following trials and as shown in Tables VIIIJ2-3 in the appendix. The 2-Week Elderly Chronic Insomnia Trials (19-047 and 190-048), the 6-week Non-Elderly Chronic Insomnia Patient Trial (190-046) and the 12-month Non-Elderly Chronic Insomnia Trials used outlier criteria for identifying subjects meeting these criteria (referred to as outliers) on laboratory parameters. Note that outlier criteria for low values on white blood cells in the differential were not employed in these trials.

Some studies also measured thyroid function levels, but the results found in the ISS were from selected studies (due to "differences in testing methods"). Estradiol was collected in three studies (190-046, 190-048 and 190-049). Generally, this review only describes the results that included interpretable on-treatment values or results that were considered potentially meaningful.

Laboratory Results Obtained from Multiple Sources. Note that safety information described below comes from multiple sources. These sources include the ISS, study reports or information provided in a 120-Date Update Report submission, as specified below.

1. Central Tendency and Outlier Results in Short-term Trials.

a) Integrated Results of Short-term, Daytime Studies (Results in the ISS). As shown in Table VIIIJ1 in the appendix most laboratory measures were collected several days post-dose (often at 5-7 days post-dose in Chronic Insomnia trials and in other trials). The incidence of outliers cannot be found from these trials. It is not clear why these trials did not include or employ pre-specified outlier criteria. Upon inquiry as to outlier data, the sponsor stated that the studies did not employ *a priori* defined criteria for identifying outliers, while maintaining that they identified subjects showing a shift in values from baseline to "end-of-study" values. Only an enumeration of subjects with laboratory values that were considered by the investigator to be "clinically significant," could be found in the ISS. Keeping these caveats in mind, only 4 out of 473 subjects (healthy volunteers) in Phase I trials (pooled) had laboratory values considered by the investigator to be "clinically significant." These 4 subjects were described as having "elevated" liver enzyme values in primarily drug-ESZ interaction studies. None of these subjects were described as dropping out of the study or having an SAE due to these abnormal values.

The ISS shows safety results in shift tables and the mean change from baseline to "End-of-Study" for integrated short-term, daytime trials. Given that most endpoint values were at several days post-treatment the study results are difficult to interpret.

b) Integrated Results of Short-term, Nighttime Studies (Results in the ISS). Laboratory analyses of data from these trials was conducted using data within 16 hours post-dose among 448 subjects in the non-elderly adult healthy volunteers in Studies 190-024 and 190-026. However, the short-term nighttime studies of Chronic insomnia patients (190-025 and 190-045) included 65 out of the total 78 subjects with endpoint treatment laboratory values at 5-7 days post-dose.

Results on outliers could not be found in the ISS from any of these pooled study categories (short-term night time studies of healthy and Chronic Insomnia patient categories, respectively). Furthermore, the results included data from a cross-over study (190-024) that was

pooled with data from a parallel group study (190-026). subjects given more than one treatment in the cross-over study "contributed to the lowest of the administered esopiclone dose categories" in the tables (on pages 136 and 138 of the ISS.pdf) showing mean change in values from baseline to "End-of-Study" or showing a shift in values. Given these limitations the laboratory results from these tables of the pooled studies 190-026 and 190-024 in the ISS, as well as results of the other pooled studies in the ISS are difficult to interpret (results on pages 135-143 in the ISS.pdf).

c) On-Treatment Laboratory Results in Selected Phase I Trials as Described in the 120-Day Safety Update Report

As, previously described the sponsor conducted additional analyses of their safety data and described their results in their 120-Day Update Submission. Since most of the results in the ISS was based on analyses of data collected after treatment cessation (sometimes days or weeks post-treatment) the sponsor reanalyzed their data to reflect on-treatment effects in short-term Phase I trials (in healthy adults) in which on-treatment data was collected (at the time-points that the sponsor selected for their analyses), as described in the following. Table VIIIJ2 and VIIIJ3 in the appendix show outlier criteria used to determine the incidence of outliers on a given parameter.

Results from Selected Daytime, Short-term (numeral 1-7 days) Studies in Healthy Volunteers (Results in the 120-Day Update).

Pooled Analysis of Data on Laboratory Assessments at 4-hours Post-dose from Studies 190-001, 190-002 and 190-005 (190-005 was conducted in elderly subjects).

Results on hematology chemistry and urinalysis parameters were generally unremarkable with some possible exceptions, as described below (only treatment groups with sample sizes of at least 24 subjects are described in the tables and in subsequent paragraphs).

Hematology and Chemistry Parameters. While mean changes in the below parameters were small, treatment group and dose-dependent trends are observed.

Table 1. Results On the Mean Change in Selected Laboratory Parameters for Studies 190-001,-002,-005 (Pooled Data, Safety Population).

	Treatment Group			
Parameter (units)	**Placebo N=58**	**1 mg ESZ N=24**	**3 mg ESZ (N=24)**	**≥3.5 mg ESZ N=40**
Baseline to Day 1 (4-hours post-dose)				
WBC (x10 ^{3}/mm^3)	- 0.04	- 0.60	- 0.58	- 0.68
Neutrophils (%)	2.80	- 0.54	- 0.62	- 0.71
Lymphocytes (%)	- 2.36	1.37	1.62	1.10
Platelet Count (x10^3/mm^3)	- 9.63	- 14.48	- 16.79	- 15.21
Baseline to Day 7 (4-hours post-dose)				
WBC (x10 ^{3}/mm^3)	- 0.33	- 0.76	- 0.36	- 0.62
Neutrophils (%)	- 1.72	0.33	-2.81	-1.59
Lymphocytes (%)	0.68	0.77	2.55	3.63
Platelet Count (x10^3/mm^3)	-8.17	-13.17	-4.94	-13.44

Results on the incidence of subjects who shifted from the normal to high or low values and the incidence of outliers were generally similar to observations from the descriptive statistical results on hematology chemistry parameters. The following table shows results on the incidence of subjects who shifted from normal to abnormal on selected parameters showing trends for treatment group effects.

Table 2. Results On the Incidence of Subjects with a Shift in Selected Laboratory Parameters for Studies 190-001,-002,-005 (Pooled Data, Safety Population).

	Treatment Group							
	Placebo N=58		1 mg ESZ N=24		3 mg ESZ N=24		≥3.5 mg ESZ N=40	
Parameter	**N to L**	**N to H**	**N to L**	**N to H**	**N to L**	**N to H**	**N to L**	**N to H**
Baseline to Day 1 (4-hours post-dose)								
WBC	1.9%	-	8.3%	-	13%	-	5%	-
Neutrophils	2.4%	9.8%	-	11.8%	-	7.1%	-	9.4%
Lymphocytes	2.4%	4.9%	4.3%	8.7%	5.3%	10.5%	-	15.2%
RBC	3.7%	-	-	-	9.1%	-	8.1%	2.7%
Potassium	1.9%	-	-	-	-	-	7.7%	-
Baseline to Day 7 (4-hours post-dose)								
WBC	-	-	-	-	-	-	-	-
Neutrophils	-	-	-	-	-	-	-	-
Lymphocytes	-	-	-	4.3%	5.3%	15.8%	-	6.1%
Basophils	-	1.8%	-	12.5%	-	4.8%	-	2.6%
Hemoglobin	1.9%	-	9.1%	-	-	-	5.4%	-
RBC	3.7%	-	-	-	9.1%	-	5.4%	-
Potassium	-	-	-	-	-	9.5%	-	-

Small treatment group and dose-dependent trends on potassium, chloride, and carbon dioxide levels were observed on the mean change from baseline to Day 1 values that did not appear to exist on Day 7. Shifts tables showed similar trends for potassium in which no subjects were identified as shifting from normal to high, but the following incidence of subjects shifted from normal to low in the placebo, 1 mg, 3 mg and ≥ 3.5 mg groups, respectively: 1.9%, 0%, 9.5%, 5.3%.

Urinalysis results on the incidence of subjects shifting from normal to abnormal and on the incidence of outliers on each parameter were provided. Results on ketones suggested a greater incidence of subjects in the high dose groups with a shift from normal to high ketones (19% and 5.4% in 3 mg and ≥ 3.5 mg ESZ groups, respectively) and outliers for high ketone levels (4.2% in the 3 mg group) compared to placebo (1.9%, 1.7% in the incidence of subjects with a normal to abnormal shift, or meeting outlier criteria for high levels, respectively).

The sponsor also analyzed data from the last line-drug assessment on each parameter and provided descriptive statistical results (including mean change from baseline to the last on-drug evaluation), and the incidence of subjects who shifted from normal to abnormal or were outliers on a given parameter. These results were similar to those already described above.

Pooled Analysis of Data on Laboratory Assessments within 24-hours Post-dose from Studies 190-001, 190-002, 190-005, 190-010, 190-011, 190-015, 190-019, 190-020, 190-024, and 190-026 (190-005 was conducted in elderly subjects).

Results generally fail to reveal any remarkable or were drug-related effects on most parameters, with possible exceptions as described in the following. In summary, the results shown below are generally similar to the results obtained from the previous analyses using data from Studies 190-001,-002, and Day -005, noting that data from these same studies were included in the above described results of an analysis on pooled data from 10 total studies. It is important to note that when pooling data from multiple studies, between subject, and between treatment group variance is likely to be great, whereby potentially masking treatment group effects, unless the magnitude of the effect were sufficiently large.

Hematology and Chemistry Parameters. While mean changes in the below parameters were small, treatment group and dose-dependent trends are observed.

Table 3. Results On the Mean Change in Selected Laboratory Parameters for Studies 190-001,-002,-005,-010,-011,-015,-019,-020,-024, and-026 (Pooled Data, Safety Population).

	Treatment Group				
Parameter (units)	**Placebo N= 186**	**1 mg ESZ N= 71**	**2 mg ESZ N= 152**	**3 mg ESZ N=183**	**≥3.5 mg ESZ N= 152**
Baseline to the Last On-drug Evaluation					
WBC ($x10^3/mm^3$)	-0.19	-0.32	-0.75	-0.58	-0.67
Neutrophils (%)	-2.17	-2.84	-4.88	-5.23	-5.34
Lymphocytes (%)	1.86	2.33	4.20	4.10	4.99
Platelet Count ($x10^3/mm^3$)	-8.79	-7.65	-10.54	-5.95	-10.88

Results on the incidence of subjects who shifted from the normal to high or low values and the incidence of outliers were generally similar to observations from the descriptive statistical results on hematology chemistry parameters. The following table shows results on the incidence of subjects who shifted from normal to abnormal on selected parameters showing trends for treatment group effects.

Table 4. Results On the Incidence of Subjects with a Shift in Selected Laboratory Parameters for Studies 190-001,-002,-005,-010,-011,-015,-019,-020,-024, and-026 (Pooled Data, Safety Population).

	Treatment Group									
	Placebo N=186		**1 mg ESZ N=71**		**2 mg ESZ N=183**		**3 mg ESZ N=183**		**≥3.5 mg ESZ N=153**	
Parameter	**N to L**	**N to H**	**N to L**	**N to H**	**N to L**	**N to H**	**N to L**	**N to H**	**N to L**	**N to H**
Lymphocytes	1.9%	3.8%	1.5%	4.5%	0.7%	4.2%	1.8%	5.8%	1.4%	8.5%
Monocytes	0.6%	1.8%	-	10.1%	1.4%	6.3%	6.1%	7.4%	1.4%	4.3%

The table below shows the results on the incidence of outliers on selected parameters.

Table 5. Results On the Incidence of Outliers on Selected Laboratory Parameters for Studies 190-001,-002,-005,-010,-011,-015,-019,-020,-024, and-026 (Pooled Data, Safety Population).										
	Treatment Group									
	Placebo N=186		1 mg ESZ N=71		2 mg ESZ N=183		3 mg ESZ N=183		≥3.5 mg ESZ N=153	
Parameter	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**
WBC	-	-	-	-	1.3%	-	2.2%	-	0.7%	-
Monocytes	-	-	-	1.4%	-	0.7%	-	1.1%	-	-

Urinalysis results on the incidence of subjects shifting from normal to abnormal and on the incidence of outliers on each parameter were provided and generally unremarkable.

2. Central Tendency and Outlier Results in 2-Week and 6-Week Trials.

a) 2-week and 6-week Trials (190-046, 190-047 and 190-048) as Described in the ISS.

Unlike the short-term trials, results on the incidence of outliers were provided for the 2 to 6 week trials, but these results are generally difficult to interpret due to the majority of laboratory values being collected 5-7 days after treatment endpoint (as shown in Table J.1).

The results from the study report for the non-elderly 6-week Chronic Insomnia Study 190-046 is described in this paragraph. Because, this trial showed greater incidence of AEs of infection in ESZ subjects compared to placebo subjects, the following results on white cell parameters are noted. The incidence of a normal to high shift from baseline to end-of-study (at 7-9 days post-treatment) was greater in ESZ subjects compared to placebo on monocytes and on basophils. However, the incidence of outliers on any given laboratory parameter was less than 1% of subjects, while noting that outlier criteria for low values on differential white cells were not employed in the trial, as in other trials.

Results on the mean change from baseline to any post-randomization time-point cannot be found in the study report for Study 190-046.

3. Central Tendency and Outlier Results from 6-Month Double-blind Phase of the Longterm Study 190-049 in Non-Elderly Chronic Insomnia Patient

a) Results as Described in the ISS.

Before describing the results on laboratory parameters, it is important to note the following aspects of screening subjects for eligibility in this trial:

- Subjects with positive results on hepatitis B or C screening were excluded from the study.
- Stringent criteria for screening out subjects with active thyroid disease were employed (including the requirement of thyroid scans in all subjects with evidence for active disease).
- Subjects "at risk of lung cancer" were required to have a negative chest x-ray for "lung cancer" within 12-monthths of study entry.
- Females "at risk for breast cancer" had to have a negative mammogram.

Mean change from baseline to the end of the study (the last non-missing value during the double-blind treatment period) and incidence of outliers failed to show any remarkable values or clear treatment group differences (between placebo and the 3 mg ESZ groups). These results are shown in Tables VIIIJ4-5 in the appendix as provided by the sponsor.

The study report in the original submission describes results over time during the double-blind treatment phase (by monthly visits). These results were also provided in the 120-Day Update Report submission and are described in the subsection below.

b) Results as Described in the 120-Day Update Submissions of data from the 6-Month Double-blind Phase of the Longterm Study 190-049 in Non-Elderly Chronic Insomnia Patients

The update report submission provides results of the mean change from baseline to each monthly visit on each hematology and chemistry parameter, as well as thyroid function parameters. These results were generally unremarkable with a few exceptions.

Perhaps the most remarkable observation are the results on platelet count in which the placebo group consistently shows greater mean changes at each monthly visits than were observed in the 3 mg ESZ group, as shown in the table below.

Table 6. Mean (±SD) Changes From the Baseline to Each Monthly Visit During the 6-Month Double-blind Phase of Study 190-049 on Selected Laboratory Parameters (Safety Population)

Parameter (Units)	Placebo N = 195	3 mg ESZ N = 593
Platelet Count ($x10^3/mm^3$)		
Month 1	-2.06 (49.6)	-4.31 (34.8)
Month 2	2.68 (46.7)	-3.76 (34.6)
Month 3	10.70 (43.2)	1.88 (35.4)
Month 4	18.19 (57.9)	1.80 (38.4)
Month 5	13.4 (42.8)	0.91 (37.6)
Month 6	11.12 (40.66)	1.26 (45.1)
Last On-Treatment Visit	4.77 (41.8)	-0.73 (44.1)

Small trends for a greater mean decrease on WBC count were observed in the 3 mg ESZ group compared to the placebo group at each monthly visit, which was generally consistent over time. However, the mean decrease was small in magnitude, as observed in the shorter-term trials described above. Similar trends appeared to exist for neutrophils (%).

Results on the incidence of subjects who shifted from normal to abnormal values at each monthly visit in each treatment group failed to reveal any remarkable findings. Results on estradiol are not described since the study was not adequately designed for examining potential effects of the study drug on estradiol or other reproductive hormones.

4. Central Tendency and Outlier Results of the Open –Label Phase of the Longterm Study 190-049 in Non-Elderly Chronic Insomnia Patients.

a) Results From the Study Report

Note the previously described stringent screening criteria for determining eligibility for participation in this trial (regarding thyroid, lung and breast screening/imaging tests, particularly in subjects "at risk" for "cancer").

Results of the open-label phase were found in the study report of the original submission. Treatment groups were generally similar on mean and median baseline values and in the median or mean change from baseline to each monthly visit on each hematology, chemistry and urinalysis parameter.

One important caveat regarding the interpretation of these results, is that they appear to simply be reflecting the mean change from the last study visit during the double-blind phase (when subjects are still receiving their assigned study drug) to each study visit of the open label phase, rather than using values collected on the actual baseline visit prior to randomization to double-blind treatment. Consistent with this interpretation is the notation found in summary tables in the study report, the "baseline" value shown in these tables were data collected "on or prior to the date of administration of the first dose of open-label study medication." Therefore, the results provided by the sponsor appear to reflect mean changes within the six-month open-label phase (in which some subjects were already on study drug at "baseline"), rather than mean changes over a 12-month period.

Results on the incidence of outliers on hematology, chemistry and urinalysis parameters during the open-label phase of the study were only described (found in the in-text sections of the study report) for open label subjects categorized into two subgroups: subjects previously exposed to placebo double-blind treatment (referred to as the placebo subgroup) and subjects previously exposed to double-blind ESZ treatment (the ESZ subgroup). These results are shown in Table VIIIJ6 in the appendix. These subgroups generally showed a low incidence of outliers on each parameter and were generally similar in the magnitude of the incidence on a given parameter.

The following parameters are noted since they showed either of the two following patterns (based on results from Tables VIIIJ5 and VIIIJ6, as described in more detail in the following). The first observed pattern was that the incidence of outliers of the ESZ subgroup <u>during the ESZ open-label phase</u> exceeded 1% (using values from Table VIIIJ6 showing open-label phase results) and was at least twice the incidence of the placebo group <u>during the double-blind treatment phase</u> (using values from Table VIIIJ5 showing double-blind phase results). The other observed pattern was that the incidence of outliers <u>during the open-label phase</u> in the ESZ subgroup exceeded 5% and was also numerically greater than the incidence <u>during the double-blind phase</u> in the placebo group (the open-label phase incidence in the ESZ subgroup shown in Table VIIIJ6 and the double-blind phase incidence in the placebo group shown in Table VIIIJ5 are provided below):

- Low monocyte count (2.2%, 0.3%, in ESZ and placebo groups, respectively).
- High monocyte count (1.7%, 0%).
- Uric acid, in females (2.2%, 0%).

<u>5. Central Tendency and Outlier Results in Elderly Chronic Insomnia Trials (Two 2-Week Trials 190-047 and 190-048).</u>

a) Results as Described in the Study Reports.

Even though Studies 190-047 and 190-048 were similar in studies design (except that one employed PSG measures in the other study used entirely subjective measures), pooled safety results from these two trials could not be found in the ISS. The following describes laboratory results for each of the trials based on information in the study reports. Subjects testing positive for hepatitis B and C were excluded from these trials.

Results from Study 190-047. Mean and median values in each chemistry and hematology parameter were provided, although, the median or mean change in parameters from baseline to the end-of-study visits could not be found in the study report. It should also be noted that values shown were for each of these two visits, in which the latter visit only occurred five to seven days after the last dose of study drug. The results shown in tabular form as end-of-text tables failed to reveal any remarkable results. The shift table results showed an incidence of a shift from normal to abnormal (from baseline to the end-of-study visit) in ESZ group that was at least twice that incidence in the placebo group were the following:

- Glucose levels: normal to high shift in 3.2% and 5.4%, of placebo and ESZ subjects, respectively.
- Urinary glucose: normal to abnormal shift in 0% (0/128 placebo subjects), 2.2% (3/136 ESZ subjects).
- Urinary ketones: normal to abnormal shift in 0.8%, 1.5%.
- Urinary blood: normal to abnormal shift in 1.8%, 9.7%.
- Basophil count: normal to high shift in 3.4%, 6.3%.

The following results on the incidence of outliers are noted in the following (parameters showing at least 1% of outliers in ESZ subjects and also at least twice the incidence observed in placebo subjects):

- High glucose (1.6%, 2.2% in placebo and ESZ subjects, respectively).
- High BUN (0.8, 2.2%).
- High urinary glucose (0.8 %, 2.9%).

Results from Study 190-048. Descriptive statistical results are provided on laboratory parameters of Study 190-048. However, results on the mean or median change from baseline to either or each study visit or to the end of the study visit could not be found. These results failed to show clinically consistent or remarkable findings. Shift tables were provided in which the incidence of subjects with abnormal urinary blood was 7.5%, 18.1% and 7.6% in the placebo, 1.0 mg, and 2.0 mg ESZ groups, respectively. The sponsor describes results on outliers but summary tables on the incidence of outliers cannot be found. The study report (section 12.4.2.3) does not describe any remarkable findings on outlier results.

6. Results Provided in the 120-Day Update Submission on Laboratory Parameters at Week 1 of Double-Blind Treatment in Two Elderly Trials of Healthy Subjects and Patients with Chronic Insomnia (pooled data from Studies 190-005 and 190-048, respectively).

The 120-Day update report provided results from the two elderly trials, pooled using on-treatment data (at Week 1 of the Double-blind treatment phase of these 2-week trials). However, a major caveat in interpreting these results was that the data was pooled from a Phase I trial of healthy elderly adults and from a Phase III trial conducted on elderly patients with Chronic Insomnia.

Descriptive statistical results failed to reveal any remarkable findings, although there were some small trends for a possible drug-related and dose-dependent effect on (treatment groups were placebo, 1 mg and 2 mg ESZ groups with approximately 80-90 subjects in each group):

- Decreasing WBC count and in decreasing % neutrophils.

While, studies were not adequately designed to examine potential effects of reproductive hormones, the following results on estradiol are most notable:

- The mean change in estradiol (pg/ml) in post menopausal women was -6.50 in placebo subjects compared to 34.50 and 13.90 in the 1 mg and 2 mg ESZ groups, respectively (sample sizes of post-menopausal women in these groups were not provided).

Results on the incidence of subjects who shifted from normal to abnormal on a given parameter were generally unremarkable or inconsistent. The most remarkable observations were the following:

- The only shift in hemoglobin that was observed in any of the treatment groups was a shift from normal to low in 5.1% of subjects in the high dose ESZ group (the 2 mg group) and no subjects with a shift in other groups.
- 5.2% of 2 mg ESZ subjects also showed a normal to high shift in glucose compared to no subjects showing a shift in the other groups.

Results on the incidence of outliers were also generally unremarkable or failed to show consistent trends. The only parameter showing trends for higher incidence in ESZ groups was the following:

- High Glucose outliers. No subjects in any of the groups were outliers for low glucose levels, while the incidence of outliers with high glucose levels in placebo, 1 mg and 2 mg ESZ groups, respectively was as follows: 3.3%, 3.8%, and 4.7%.
- Outliers on several thyroid function tests were also common in which the following parameters showed possible trends for a drug-related and dose-dependent effect (the incidence in placebo, 1 mg and 2 mg ESZ groups, respectively, are shown):
    - High T3 Uptake (5.0%, 9.7% 13.9%)
    - Low TSH (6.3%, 5.6% 11.4%)

7. Special Laboratory Parameters.

Special Laboratory Parameters.

As previously described thyroid function test results provided in the ISS were from only a selection of studies (in the incidence of outliers and results on central tendency). Estradiol levels were obtained in three studies (190-046, 190-048 and 190-049), but these trials were not designed to examine the effects of the study drug on reproductive and function or hormonal changes. As shown in Table VIIIJ1 in the appendix laboratory measures were often collected days after cessation of treatment. The following summarizes results of thyroid function tests in the selected trials.

While group differences may appear to exist for some parameters in some of the studies, these differences were not consistent across studies and were generally not consistent across treatment groups or among parameters (e.g. when comparing treatment group results on TSH to results on T4). However, failure to show consistent or clear treatment group effects may be inherent to the limitations in the methodology of these studies. These limitations include failure to have "on-treatment" values in some of the studies, the use of a single value rather than multiple values over time, time-dependent fluctuations in hormonal parameters, among others.

The 6-week study 190-046 in non-elderly adults with insomnia used the 3 mg dose level but obtained laboratory measures 5-7 days post-dose (after the double-blind treatment phase).

Yet, this trial showed an incidence rate of outliers for high TSH levels of 4% in placebo, 9% in the 2 mg group and 11% in the 3 mg group compared to 1 to 3% of subjects with low values among these groups. However, the groups were similar on T4 outliers and the results on the mean change from baseline values failed to show marked or clear treatment group effects. These results are shown in Table VIIIJ7 in the appendix.

The results from the 6-month double-blind phase of the longterm patient study (190-049) on mean change in estradiol levels are shown in Table VIIIJ7 in the appendix (as provided by the sponsor).

Tables VIIIJ5 and VIIIJ7 show results on outliers on TFT parameters. In summary a large incidence of outliers occurred (>5% and in some cases >10%) with some possible drug-related patterns as will be described in more detail in the following. However, it is important to note that while these results may suggest a potential effect of ESZ on TFTs, the study was not adequately designed for examining such potential effect exists (i.e. not well controlled to enhance sensitivity and specificity, stringent screening/eligibility criteria for thyroid disease and thyroid scans were required of all subjects with active disease, among others). Secondly, mean or median changes in TFT parameters over time showed minimal to no changes and treatment groups were similar results. Shift tables also failed to reveal treatment group differences on shifts from baseline to at the End-of-Treatment (not clear if subjects were still on treatment at this time-point). As described in previous sections, one subject was an adverse dropout during the ESZ open-label phase of the trial, due to "thyroid disorder" with a "nodule," the following related AE's were reported in ESZ subjects during the double-blind phase (but not in placebo subjects unless otherwise specified): goiter in 3 ESZ subjects, hypothyroidism in 3 ESZ subjects (1 placebo S) and parathyroid disorder in 1 ESZ S. For additional subjects had the AE of hyperthyroidism (two subjects), hypothyroidism (one subject) and thyroid disorder (one subject) during the open label phase of the trial.

Given the methodological limitations of Study 190-049 and the high variability (between and within subject variance) on test parameters (likely to be reflecting to the inadequate study design for examining thyroid function), and the potential effect of ESZ on thyroid function remains unclear.

A detailed discussion of a potential drug-related pattern on the incidence of outliers on TFT parameters (based on results of Tables VIIIJ5-7) is provided in this paragraph and in paragraphs that follow. The incidence of outliers on thyroid function tests were generally at least 5% or greater in any given treatment group. During the double-blind treatment phase the treatment groups were generally similar on these parameters. Perhaps the magnitude in the incidence of outliers is reflecting a large variance in each of these parameters or "background noise," suggesting that this study was not well-controlled in minimizing this variance (i.e. the study was not designed to specifically examine potential drug effects on thyroid function).

Despite, the limitations in the study design relevant to revealing potential effects of thyroid function, the incidence of outliers on thyroid function test parameters during the open label phase were even greater than that observed during the double-blind treatment phase (placed on numerical comparisons of the results). These results could be reflecting long-term monitoring of subjects independent of the study drug. However, when comparing the incidence of outliers are the open-label subgroup of subjects who were previously exposed to double-blind ESZ treatment, to the incidence of outliers in the placebo group of the double-blind treatment phase, the following results are noted (incidence during the open label phase of the subgroup of subjects

previously exposed to double-blind ESZ treatment and the incidence in the placebo group during the double-blind phase are provided):

- Low T3U (12.6%, 1.5%)
- High T3U (20%, 14%).
- High T4 (3.6%, 1.0%)
- High TSH (8.1%, 5.6%).
- Low TSH (8.1%, 5.6%).

Additionally, most of the above parameters showed an incidence in the subgroup of open-label subjects who were previously exposed to double-blind placebo treatment that was either similar to or greater than the subgroup of open-label subjects previously exposed to double-blind ESZ treatment. The incidence on this open-label subgroup (the subgroup previously exposed to double-blind placebo treatment) on each of the above parameters are shown below:

- Low T3U (4.5%)
- High T3U (12.6%).
- High T4 (3.6%)
- High TSH (6.3%).
- Low TSH (5.4%)

The sponsor provided the incidence of outliers during the "first 6 months" of ESZ treatment in a subgroup of subjects who received at least one dose of either, open label or double-blind ESZ (data from subjects of the ITT Safety population who were randomized to double-blind ESZ treatment combined with data from ITT Safety subjects randomized to placebo double-blind treatment who entered the ESZ open-label treatment phase). This subgroup of subjects showed an incidence on each thyroid function test parameter that was generally similar to placebo treated subjects (using data from Table VIIIJ5 of the placebo group during the double-blind treatment phase) except for the following parameters with the incidence shown for the subgroup:

- High T3U (17%).

The sponsor provided the incidence of outliers during ESZ treatment of "up to 12 months" in duration (ITT Safety subjects who at least one dose of double-blind ESZ and the ITT safety subjects who were assigned to the ESZ group during the double-blind treatment phase, who then entered the open label phase). The following results are noted for numerical comparisons to results, above for various subgroups during the double-blind and open label phases of the trial:

- Low T3U (6%)
- High T3U (22%).
- High TSH (8%).
- Low TSH (9%)

Note that the incidence of these subjects on each of the above parameters was similar to the incidence observed in the open-label subgroup of subjects previously exposed to double blind ESZ treatment. Furthermore, the incidence was numerically greater than the incidence of the open-label subgroup of subjects previously exposed to double-blind placebo treatment on each corresponding parameter, as well as, the incidence in placebo subjects during the double-blind phase of the trial on each parameter.

8. Laboratory Results of Special Population Studies (Renally or Hepatically Impaired Subjects, Studies 190-013 and –014 and Subjects with a history of Benzodiazepine Abuse, Study 190-016).

The ISS provided results on the mean change from baseline to 72 hours or 120 hours post dose values (respectively) in laboratory values from renally impaired (given 3 mg ESZ) or hepatically impaired groups (given 2 mg of ESZ) in the single dose Phase I studies 190-013 or 190-014, respectively. The study groups were normal, mild, moderate and severe groups (regarding the degree of hepatic or renal impairment). Since all subjects received the same treatment (a single dose of ESZ) and there was no placebo treatment employed, any group differences revealed on the mean change of values may be reflecting a drug by degree of impairment interaction effect on a given parameter. However, other confounding variables must also be considered, since these studies were not adequately designed for revealing potential drug related or drug by degree of impairment interaction effects on the change in parameters. Also consider the time-lag after treatment from which the post-baseline values were obtained. The median and range of values and results of baseline values could not be found in the ISS.

a) Study 190-013 on Hepatic Impairment: Results on Laboratory and Urinalysis Parameters. Results, as above, were generally unremarkable or not unexpected for subjects with hepatic dysfunction (i.e. up to a mean increase of 13±30 U/L of a hepatic enzyme) except for results on platelet count and glucose levels and urinalysis results on comparable parameters (blood and glucose). The results are shown in the tables below.

Study 190-013. Mean(±SD) Changes from Baseline to the End of the Study (on Day 6, 120 hours after a single dose of 3 mg ESZ) for Selected Laboratory Parameters

	Hepatic Function Group			
Hematology/Chemistry Parameter	**Normal (N=16)**	**Mild (N=8)**	**Moderate (N=8)**	**Severe (N=8)**
Platelet count ($x10^9$/l)	-0.6 (±30.7)	8.8 (±19.9)	-1.4 (±23.2)	-8.7 (±15.9)
Glucose (mg/l)	-3.3 (±6.5)	1.5 (±20.3)	7.0 (±7.15)	5.9(±45.1)

Note that moderate and severe groups showing numerically greater decreases in platelet count and greater increases in glucose than normal and mild groups. 1 S in each of these two more severely impaired groups also had a shift in glucose from normal to abnormal on their urinalysis test, as below. Also white blood count shifted to normal to abnormal in these higher dose groups. These effects could be reflecting a drug by degree of liver impairment, interaction effect.

The sponsor concludes that the results on glucose is reflecting the distribution all of subjects of diabetes across the study groups. 38% of subjects (3/8 subjects per group) in the moderate and severe groups had diabetes mellitus, no subjects in the other groups had diabetes. However, glucose levels for these individual subjects or for diabetic and non-diabetic subgroups could not be found in the ISS. If elevations only occurred in the diabetic subjects then one must also consider a role of study drug on glucose levels in the diabetic and hepatically impaired population. The sponsor describes their PK results as showing approximately a 74% increase in AUC and an increase in T ½ to 14 hours in the severe group, such that results on the above laboratory parameters may be reflecting a drug effect in which the moderate and severe groups have greater systemic exposure due to impaired metabolism of the parent and active drug.

Study 190-013. Common Shifts (≥5% in any group) from Normal (N) at Baseline to Abnormal (A) at the End of the Study (Day 6, 120 hours after a single dose of 3 mg ESZ) on Urinalysis Parameters				
	Hepatic Function Group			
	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Urinalysis Parameter n (%)	N to A	N to A	N to A	N to A
Blood			1 (13%)	2 (25%)
Glucose			1 (13%)	1 (13%)
Protein			1 (13%)	

2 subjects had abnormal laboratory parameters at post-dose (WBC of 1.54 x109/l in S 231031 and glucose of 158 mg/dl in S328001), but had normal values at baseline (WBC of 7.08x109/l in S 231031 and glucose of 95 mg/dl in S328001). S 231030 and S 231036 had low sodium (as low as 128 mEq/l) and low WBC count ($1.48x10^9$/l), respectively but they also had low values at baseline (S231030 had sodium level of 130 mEq/l; S231036 had WBC of 3.67 x 10^9/l).

b) Study 190-014 on Renal Impairment: Results on Laboratory and Urinalysis Parameters. Results that were provided (as previously described) for Study 190-014 on subjects with impaired renal function were generally similar to those of subjects of Study 190-013 with hepatic function impairment. Results were generally unremarkable, except for platelet count and glucose levels and some of the urinalysis parameter results, as shown below. As in study 190-014 the majority of diabetic subjects were in the moderate and severe renal function groups (63% or 5/8 subjects in each group) compared to no normal subjects and 13% (2/8subjects) of the mild group who were diabetic. Only one S was an outlier on a parameter, which was on glucose levels (the value cannot be found in the ISS).

Study 190-014. Mean(±SD) Changes from Baseline to the End of the Study (on Day 4, 72 hours after a single dose of 3 mg ESZ) for Selected Laboratory Parameters				
	Hepatic Function Group			
Hematology/Chemistry Parameter	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Platelet count ($x10^9$/l)	8.9 (20.4)	4.1 (36.6)	-11.9 (26.7)	-15.5 (24.0)
Glucose (mg/l)	-1.6 (19.09)	7.5 (28.90)	33.0 (52.86)	35.4 (48.93)

Study 190-014. Most Frequent (≥5% of subjects in any group) Shifts from Normal (N) to Baseline to Abnormal (A) at the End of the Study (on Day 4, 72 hours after a single dose of 3 mg ESZ) on Urinalysis Parameters				
	Hepatic Function Group			
	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Urinalysis Parameter n(%)	N to A	N to A	N to A	N to A
Blood	1 (6.25)	1 (12.50)	3 (37.50)	3 (37.50)
Glucose			4 (50.00)	5 (62.50)
Protein		2 (25.00)	4 (50.00)	7 (87.50)

Some effects of renal function on PK parameters (an 8-25% increase in Cmax and a 29-47% increase in AUC) are described by the sponsor but there is substantial overlap of the individual PK values between the groups. Given these potential effects of renal function on PK, one cannot rule out a potential drug by renal impairment effect on the above abnormalities or

possibly an effect of the drug on glucose levels in diabetics. Actual mean change in diabetics versus non-diabetics was not described in the ISS, such that one cannot assume that observed pattern in the mean change of glucose across renal function groups was due to the skewed distribution of diabetics toward the more renally impaired study groups.

Note that group differences on the above laboratory/urinalysis parameters appeared to be numerically greater than group differences on most of these parameters in the hepatic function study, 190-013. Perhaps greater group differences in the renal function study is due to a higher dose of ESZ (3mg) and values being collected sooner (72 hours) post-dose, than employed in the hepatic function study (used a 2 mg dose and collected data at 120 hours post-dose). These observations are suggestive of a potential role of study drug on platelet count, blood in urine (which could be due to low platelet levels) and glucose levels and glucose in the urine. However, the interpretation of study results is compromised by the limitations of the study design employed in these studies and in the absence of other data.

c) Results of Study 190-016 on Subjects with a History of Benzodiazepine Abuse. This study was a 6-way cross-over study of placebo, 3 mg, 6 mg and 12 mg ESZ and 10 and 20 mg diazepam single-dose treatment conditions in 28 subjects with a history of benzodiazepine abuse. No data is provided by treatment condition that can be found in the ISS. A summary shift table is provided but results are for all subjects combined independent of treatment and are not interpretable in terms of a potential drug-related effect on a given parameter. None of the subjects had values considered clinically significant or had abnormal values that lead to an adverse dropout.

K. Results on Vital Sign, Temperature and Body Weight Parameters

Table VIIIK1 in the appendix provides the outlier criteria employed for identifying outliers on vital signs and other parameters.

Since outlier data was not consistently described or found and summary shift tables were generally provided instead (as previously described for laboratory parameter results), some of the results from summary shift tables that are considered to provide some potentially meaningful observations are described below, as specified.

Note that the outlier criteria shown in Table VIIIK1 in the appendix do not include criteria for outliers and orthostatic measures, as most if not all efficacy trials did not include orthostatic measures in the protocol.

Table VIIIK2 shows time-points when vital sign was collected in each study listed under each study-type category. Note time-points were generally over four half-lives of the study drug, with only a few exceptions.

Results Obtained from Multiple Sources. Results described below include those found in the ISS, and in some cases, were found in a study report, as specified.

As previously described, the 120-Day Update submission provided some results of an additional analyses that were conducted using on-treatment data from selected trials, as specified below.

1. Vital Sign Results in Short-term Trials.

a) Results from Short-term Trials in the ISS.

As shown in Table VIIIK2 short-term trials had vital sign and temperature data collected anywhere from 1 day to 20 days post-dose in daytime trials and from 8 to 48 hours post-dose in night time trials. Given these data collection time-points and the Tmax and T1/2 of ESZ (1 hour and 6 hours, respectively) the vital sign results in these trials, as shown in the ISS are limited and difficult to interpret (as presented on pages 189-198 of the ISS.pdf). Post-dose values in these short-term trials are not likely to reflect on-treatment effects or to be adequately sensitive in detecting a potential treatment effect, since time-points exceed Tmax by several hours or several days. Examination of tables on the incidence of subjects meeting outlier criteria, where provided in the ISS failed to reveal any remarkable treatment group differences.

b) Results from Short-term Trials in the 120-Update Submission.

Vital Sign Results at 30-120 Minutes Post-Dose or at 0-6 Hours Post-Dose in Shorts-Term (1-7 Days) Trials (Studies 190-001,-002,-005,-010,-011,-012,-015,-018,-019,-020, and-023, data pooled).

Only the results of treatment groups with a sample size of at least 24 subjects are described in this review.

A small trend for a dose-dependent increase in the mean change from baseline to the 30-120 minutes post-dose assessment on heart rate was observed, particularly for the two high-dose ESZ groups (3 mg and ≥ 3.5 mg groups). And even greater trend was observed on the mean change from baseline to the 0-6 hour post dose analysis, as described in the following:

- Mean change in heart rate from baseline to 30-120 minutes post-dose: The mean change (±SD) in heart rates (in units of beats/minute) in the placebo (n = 124), 1 mg (n = 24), 2 mg (n = 52), 3 mg (n = 123) and ≥3.5 mg (n = 91) ESZ treated subjects were as follows: 0.2 (6.5), 1.2 (5.3), -0.1 (6.8), 1.5 (7.0), and 3.7 (9.0), respectively.
- Mean change in heart rate from baseline to 0-6 hours post-dose: Even greater trends were observed on the mean change from baseline to the 0-6 hour postdose analyses on heart rate in the two high-dose groups as follows: a mean change of 1.5 (±6.1), 1.0 (±5.4), 2.5 (±6.4), 4.6 (±8.1) in the placebo, 1 mg, 2 mg, 3 mg, and ≥3.5 mg groups, respectively.

Trends for a dose-dependent decrease in both systolic and diastolic blood pressure were also observed as follows:

- The mean change (±SD) from baseline to the 30-120 minutes post-dose assessment on systolic blood pressure (mmHg) in the placebo, 1 mg, 2 mg, 3 mg and ≥3.5 mg ESZ groups was 1.0 (8.4), -1.5 (5.2), -6.3 (8.8), -5.9 (8.8), and -3.1 (8.2), respectively.
- Smaller numerical trends for decreasing diastolic pressure in ESZ groups were also observed.
- Similar results were observed on the mean change from baseline to 0-6 hour postdose analyses on these parameters.

2. Vital Sign Results of the 6-week Study 190-046

a) Results from the 6-week Study 190-046 in the ISS or Study Report.

Mean change from baseline to "the last non-missing post-baseline value or before end-of treatment visit" values were provided (no range or median values) and the incidence of outliers failed to reveal any remarkable values or any clear treatment group effects.

Results from the study report for the non-elderly 6-week Chronic Insomnia Study 190-046 showed the following. Somewhat greater incidence of outliers in ESZ compared to placebo subjects on low blood pressure and heart rate (but treatment group differences were not clinically remarkable). Results on the mean change from baseline to any post-randomization time-point cannot be found in the study report.

3. Vital Sign Results of the 6-month Double-blind Treatment Phase of Study 190-049

a) Results of Double-Blind Phase of Study 190-049 Described in the ISS or the Study Report

The results provided for the 6-month double-blind treatment phase of this study were similar to those in nature to those that were provided for the 6-week study (using "the last non-missing post-baseline value or before end-of treatment visit" for obtaining mean change from baseline to "end-of-treatment" values). These results also failed to reveal any remarkable values or any clear treatment group effects (on both incidence of outliers or on mean change from baseline to treatment endpoint values).

The study report provides the median and mean changes from baseline to each study visit (Visits 5 and 8) and the incidence of outliers in each treatment group on each vital sign parameter (sitting heart rate and blood pressure, respiratory rate, temperature and weight). In summary, the results were unremarkable and the treatment groups were similar on each parameter.

This study did not include orthostatic vital sign measures, as the protocol was amended to exclude these measures, since subjects were being examined near, or at, trough drug levels.

4. Vital Sign Results of the 6-month Open-Label 3 mg ESZ Treatment Phase of Study 190-049

Descriptive results that included the mean change from baseline to each open label phase visit (Visits 11 and 14) and the incidence of outliers during the double-blind treatment phase on each vital sign parameter were provided by the sponsor. As already described, orthostatic vital sign measures were not conducted in the study.

The vital sign results were generally unremarkable except for the following results on the incidence of outliers during the open label phase (the incidence during the open label phase, and for comparison, the incidence of the ESZ and placebo groups during the double-blind treatment phase are also provided):

- Decreased systolic blood pressure $\geqslant$20mmHg (11.3%, 9.1%, 7.7%, respectively).
- Decreased diastolic blood pressure $\geqslant$ 15mmHg (10.8%, 6.1%, 5.6%).
- Increased heart rate $\geqslant$ 15 beats/min (16.1%, 10.5%, 8 .2%)

However, when using more stringent criteria for each of the above parameters the incidence of outliers on each parameter of these was unremarkable (either 0.0% or 0.2%) in subjects during

the open label phase. The more stringent criteria employed for this reanalysis on the incidence outliers is described in the following. In addition to meeting the above criteria, the subject also had to meet cutoff criteria for the absolute value on a given parameter, as follows: < 90 mmHg systolic blood pressure, as well as a ⩾20 mmHg decrease, <50 mm Hg diastolic blood pressure, as well as a ⩾15 mmHg decrease, or a heart rate >120 bpm, as well as a 15 bpm decrease.

Vital sign results obtained for the following two subgroups of subjects were also described in the ISS:

- Subjects who received up to the "first six months" of ESZ treatment: ESZ ITT safety subjects of the double-blind phase or ITT Safety placebo subjects of the double-blind phase that entered the open-label phase).
- Subjects who received "up to 12 months" of the ESZ treatment (ITT Safety subjects who at least one dose of double-blind ESZ and the ITT safety subjects who were assigned to the ESZ group during the double-blind treatment phase, who then entered the open label phase).

The results of the incidence of outliers in these two subgroups of subjects were generally unremarkable.

5. Vital Results in Elderly Chronic Insomnia Trials (2-Week Studies 190-047 and 190-048)

a) Results of Studies 190-047 and 190-048 in the ISS. These studies conducted on elderly subjects with Chronic Insomnia had vital sign data at 8-48 hours post-dose limiting the ability to detect potential treatment group effects (given the short half-life and Tmax of the study drug in which study drug levels would be at trough or were nondetectable). No orthostatic vital sign measures were obtained in either of these trials. In Study 190-047 the vitals were taken at the end of one week of treatment (trough or non-detectable drug levels were likely to exist) and on 1-3 days after the last double-blind dose in this 2-week trial. Given these limitations, some of these results may be useful from the perspective of revealing potential withdrawal effects that may be detected in these multiple dose trials on vital sign parameters. Furthermore, the studies were conducted on elderly patients who are likely to be more vulnerable to adverse effects after cessation of treatment. Consequently, the study results are described in this review.

Results on central tendency and outliers (pages 196-197 of the ISS.pdf) revealed no remarkable treatment group differences and only a few subjects met outlier criteria (generally only 1 or no subjects in a give group).

b) Results of Studies 190-047 and 190-048 in the Study Reports. Examination of results on vital signs provided in the study reports of Studies 190-047 and 190-048 failed to reveal any remarkable findings (on descriptive statistical results by visit). Summary tables on the incidence of outliers cannot be found, but section 12.5.1 does not describe any remarkable findings on outliers.

c) Results of Studies 190-047 and 190-048 (data pooled) Using the Last On-Drug Value Described in the 120-Day Update Submission.

Descriptive statistical results using the last-on drug data were unremarkable.

6. Vital Results of Special Population Studies (190-013 and –014).
The ISS shows the mean change (±SD, but not median values or the range, or any results of baseline values) from baseline to post-dose vital sign values (heart rate, systolic and diastolic blood pressures, temperature and respiratory rate). Note that post-dose values in Study 190-013 (study of subjects with hepatic impairment) and Study 190-014 (study of subjects with renal impairment) were obtained on Day 6 of each study, which was 120 hours post-dose (as noted in the summary tables on pages 202-203 in the ISS.pdf). The results were provided for normal, mild, moderate and severe renal or hepatic function groups in which all subjects received a single dose of 2 or 3 mg of ESZ (no placebo treatment). The ISS does not describe any results on outliers or shift in values.

Given that post-dose values were obtained days after exposure to study drug (even when factoring in effects of renal and hepatic impairment on PK parameters) it is not surprising that the studies failed to show any consistent or remarkable group differences on mean change of vital sign values.

7. Vital Results of Special Population Study 190-016. This study was a 6-way cross-over study of placebo, 3 mg, 6 mg and 12 mg ESZ and 10 and 20 mg diazepam single-dose treatment conditions in 28 subjects with a history of benzodiazepine abuse. The ISS shows mean change (no other values) of vital sign values from baseline to the end of study for all subjects combined, independent of treatment. A description of vital sign data by treatment condition cannot be found in the ISS. Therefore, the results as presented in the ISS are not interpretable. The ISS does not describe any results on outliers or shift of values from baseline.

L. Results on Electrocardiographic Parameters
Almost all of the ECG results for pooled data within each study type category (of which results are primarily descriptive statistical results on ECG parameters) do not represent results from only the data that was collected during treatment or near Tmax. Instead, data from baseline and post-treatment time-points were included in the results provided in the ISS. The post-treatment values used were generally 10 hours to several days post-dose as shown in Table VIIIL3 (in the appendix) for all of the pooled results in each of the study type categories in the ISS (Table VIIIL3 and similar tables for other safety parameters were provided by the sponsor in an amendment submission in response to inquiring about the time-points used for their data analyses).

Outlier or shift summary results cannot be found for pooled data for each study-type category or if results are provided, they generally do not include on-treatment or end-of-treatment values (within Tmax or the half life of the study drug).

Therefore, most of the pooled ECG results in the ISS are not meaningful or interpretable as to whether or not the study drug has any effect on any ECG parameter. There are some exceptions, to this conclusion regarding the pooled or unpooled ECG data presented in the ISS. These exceptions, in which data was collected near Tmax or T1/2 are described in this review, below.

Results from Multiple Sources. In addition to describing selected results from the ISS, as above, results from a given study report and from the 120-Day Update Report submission are described in subsections below. The 120-Day Update report described results of EKGs identified as abnormal in the long term trial (Study 190-049). These data were reanalyzed in a

manner to describe the type of EKG abnormality revealed and to provide the incidence of subjects within a given category of EKG abnormality, as described below.

Additional clarification regarding EKG results provided in the ISS was provided in a 3-23-03 amendment submission.

1. Electrocardiographic Results at 90-Minutes Post-dose for Three of the 1-7 Day Short-term Studies in the ISS.

The time-points for ECG assessments in 3 of the 15 Phase 1 (1-7 Day studies) included assessments near Tmax of ESZ. Tmax is approximately one hour and these 3 studies had ECG assessments at 90 minutes post-dose. Two of the three studies were 7-day multiple dose studies (190-002 and 190-005) and the third study (Study 190-011) was a single-dose 2-way cross-over study. Table VIIIL4-6 summarizes results on the mean baseline and mean change from baseline to 90-minutes post-dose on each of the following days: on Day 1 of treatment for all 3 trials (Table VIIIL4), on Day 6 or 7 of treatment of the two multiple dose trials (Table VIIIL5) and on all treatment days with 90-minute post-dose values, combined for the 3 trials (Table VIIL6). No median values or range of values could be found in the ISS.

In summary, Tables VIIIL4-6 do not show any clear or consistent treatment group differences on the mean change from baseline to 90 minutes post-dose on ECG parameters. The sponsor considers the results in Table VIII5 (at Day 6 or 7 post-dose) as reflecting data collected at steady state. However, given the short Tmax and half-life of ESZ, it would not be expected that subjects would be able to achieve steady state levels on a once-a-day treatment regimen. Therefore, it is not clear the results are referred to as results reflecting ECG data collected at steady state.

The ISS also indicates that none of the 90 minute post-dose values for QTcB (Bazett's correction) interval exceeded 500 msec and only 1 S in the 2 mg ESZ group had a value over 450 msec. However, it is not clear why the sponsor chose QTcB for describing outliers, since this type of correction is more typically used when there is a drug effect on lowering the heart rate. Furthermore, previously described vital sign data revealed at least trends for an increase in mean heart rate at the 3 mg and $\geqslant$ 3.5 mg ESZ dose-levels in Phase I trials, as well as other trials (at time-points near Tmax). Therefore, these results on QTcB outliers are difficult to interpret. Only 2 ESZ subjects had a shift from normal to "clinically significant" abnormal EKGs at "end-of-study." However, a definition of "end-of-study" on page 224 cannot be found and could be at a post-dose time-point exceeding Tmax or T1/2.

2. "Clinically Significant Abnormal" ECGs in Subjects with Normal Baseline ECGs in Studies of Each Study-Type Category as Described in the ISS and a 3/23/03 Amendment Submission

In a 3/23/03 amendment submission under this NDA, the sponsor clarifies that "ALL" "clinically significant" post-baseline ECGs identified by the investigator are described in section 8./10.H.14.4 of the ISS (page 219 of the ISS.pdf). The following describes the "clinically significant" EKGs. Only two 3 mg ESZ subjects (S 172034 and S 0410008) had an ECG abnormality.[11] The type of EKG abnormality described in each of these subjects did not appear

[11]The "end-of-study" ECG abnormalities were: "abnormal sinus rhythm with occasional ventricular premature complexes and an early repolarization" in one S and the other S had an "incomplete right bundle branch block and a poor R wave progression"). The former S was only 25 years old (a black female) and the other S was a 42 year old

to be remarkable or were not atypical events of the general population. Neither S had any cardiovascular AEs and did not withdraw prematurely due to their abnormal ECG results. Therefore, these events were not likely to be drug-related.

3. Outliers on QTcB (Bazett's correction) as Provided in the ISS.

Outlier results on ECG parameters could not be found in the ISS for pooled study type categories. However, the sponsor provided a summary table of the incidence of outliers on QTcB (on page 220 of the ISS.pdf). Since bradycardic effects of the study drug did not appear to exist, it is not clear why the sponsor selected QTcB interval, particularly since trends for an increase in heart rate was observed in various trials, as previously described in this review. Nevertheless, very few subjects for each of the following pooled study-type categories had a QTcB exceeding 450 msec: Daytime 1-7 Day Trials, Nighttime, 2-week study (190-048), Nighttime 6-week study (Study 190-046) and the Nighttime 6- month study (190-049). It is not clear why other studies were not included in the summary table.

The 6-month Study 190-049 on non-elderly Chronic Insomnia patients showed incidence rates of QTcB outliers of 3.1% and 5.7% in the placebo and 3 mg groups. However, a 6-week trial (190-046) with approximately 100 subjects in each treatment group (placebo, 2 mg and 3mg ESZ groups) had only one outlier in the 2 mg group.

4. ECG Results of the Longterm Non-Elderly Chronic Insomnia Trial (Study 190-049) as Provided in Study Report.

The study report for this trial provided more information on EKG results than could be found in the ISS. Therefore, the following describes results from the study report for the 6-month double-blind and the 6-month open-label phases.

Results on the incidence of outliers could not be found, except for outliers on QT or QTc interval. EKG assessments were conducted at each monthly study visit during both the double-blind and open-label phases of the trial. Descriptive statistical results were provided for EKG parameters (RR, PR, QRS, ventricular rate, QT and QTcB, QTcF).

The results as presented by the sponsor fail to reveal any remarkable observations other than the following two observations described in the following paragraphs.

The first potentially remarkable finding is regarding the descriptive statistical results on the RR (in units of msecs). Numerical comparisons of the data from the double-blind, as well as the open-label phases appears to reveal a generally consistent mean or median change (from baseline to each monthly study visit) in the negative direction (mean changes increased from approximately -6 to up to approximately -19 msec). This pattern appeared to be more prominent in the ESZ group compared to the placebo group and became greater over time (i.e. the median or mean R-R interval generally decreased over time with ESZ treatment (based on numerical comparisons). The actual results are described in more detail in the next paragraph. The interpretation of these results and their clinical relevance is unclear. For reasons that follow the results appear to more likely be reflecting a benign phenomenon, or be an artifact, or may be a secondary effect on another parameter (i.e. on heart rate). While, the observed pattern could be drug-related, the group differences are small (values are in milliseconds) and in turn, results on

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Caucasian female. They had normal ECGs at baseline. The younger S participated in a 6-week study and the older S withdrew early due to "personal reasons."

ventricular rate expressed in units of beats per minute failed to show any clinically significant changes or treatment group differences (both groups showed minimal to no change over time). Yet, a potentially drug related effect on mean increased heart rate and on incidence of outliers, as well as potential drug effects on other vital sign parameters were previously described in this review. Nevertheless, outliers not met criteria for an increase in heart rate, generally did not meet criteria on absolute heart rate exceeding 120 bpm.

This paragraph describes results on the mean RR interval in greater detail. The mean change in RR interval (from baseline to the end of the study, in units of msecs) in the double-blind treatment phase was -6.3 and - 9.6 in the placebo and ESZ group, respectively. A greater mean decrease was observed during the open label phase (from baseline, which was the last assessment prior to the open label phase, to the end of the study), which was - 14.0. When examining results from the subgroup of the ITT safety population with up to 6 months of ESZ treatment (subject in the double-blind ESZ group and open-label subjects previously receiving placebo and the double-blind treatment phase), the RR interval was – 10. A greater mean decrease was observed in subjects receiving up to 12 months of ESZ treatment (ITT safety subjects in the ESZ group of the double-blind treatment phase, which included subjects who also entered in the open label phase) was -18.6.

Another potentially remarkable ECG finding is that a large percentage of subjects shifted from normal to abnormal EKGs in the double-blind phase (17% and 20% in the placebo and ESZ group, respectively, from baseline to the end of treatment (it is not clear if subjects were still on treatment at that time point, since some subjects were continued on open label ESZ treatment.

Similar results were revealed during the open label phase (20% of the subjects shifted from normal to abnormal, from baseline to the "end of treatment"). However, these abnormal ECGs were considered "not clinically significant" based on the clinician's assessment. Few to no subjects had a shift from normal to "clinically significant" ECGs. These results are difficult to interpret due to a number of limitations in these data, as follows. Firstly, the results during the open label phase appear to reflect a shift from a time point when subjects were completing the double-blind phase and potentially still on treatment (Table 14.3.3.1B in the study report indicates that baseline is "the last assessment on or prior to the date of administration of the first dose of the open-label study medication"). Secondly, the type of abnormal EKGs observed in these subjects was not described (EKGs were not categorized by type of abnormality). Consequently, without knowing the type of ECG abnormality, these results are difficult to interpret, other than that the clinician did not consider them to be "clinically significant" ECGs.

5. Results on Abnormal EKGs in Study 190-049 as Provided in the 120-Day Update Submission

The sponsor categorized to abnormal EKGs into the following categories:

- Rhythm: includes artificial pacemaker, atrial fibrillation, atrial flutter, ectopic atrial rhythm, ventricular bigeminy, and other.
- Arrhythmia including APC and VPC.
- Conduction: including first degree block, IRBB, IVCD, LAH, RBBB, and LPH.
- Morphology including LAA, LVH, RAA, and RVH.
- Myocardial infarction.
- ST segment
- T waves
- U waves

The sponsor provided the incidence of subjects in each treatment group of Study 190-049 with each category of EKG abnormality for each month of the visit, as well as on the last-on-treatment visit. These results failed to reveal any remarkable findings.

No other new or remarkable ECG results were provided in the safety update report.

6. ECG Results in Elderly Chronic Insomnia Trials (2-Week, Studies 190-047 and 190-048) as Provided in the ISS.

Study 190-047 did not have any post-dose ECG assessments (only an ECG at screening). Study 190-048 conducted ECG assessments at trough or non-detectable levels of study drug at the end of week 1 of treatment and on 1-3 days after the last dose of double-blind treatment in this 2-week trial. Descriptive statistical results were provided for each study visit (baseline, week one visit, and the end-of-study visit at 1-3 days post-dose). However, the median or mean change in values from baseline to each study visit cannot be found. The incidence of outliers could only be found for QTcB interval results. The results that were provided fail to reveal any remarkable or *clinically significant findings.*

M. Subgroup Analyses of Clinical Safety Parameters

Subgroup Analysis by Age, Gender, and Ethnicity.

The sponsor describes a subgroup analysis of vital sign parameters (blood pressure, heart rate and temperature) on the basis of age by comparing old and young age-groups (< 65 and ⩾ 65 -year-old groups, respectively) on a given parameter using data from the 2 and 6-week trials of patients with chronic insomnia (data pooled).

In summary the sponsor provides values within the text section of the ISS that do not show any clinically remarkable age group differences in mean values on each vital sign and temperature measures. However, there are number of caveats regarding the interpretability of these results, as described in the following. First, it should be noted that orthostatic vital sign measures were not obtained in these trials (due to the time-points for vital signs assessments relative to dosing). Secondly, age-group numerical comparisons (statistical comparisons were not conducted) were in essence comparisons between of subjects across studies, as follows. The trials from which data was pooled to conduct this analysis were two 2-week trials in elderly patients (190-047,-048) and a 6-week trial on nonelderly patients space (190-046), such that a comparison between the young and old groups was a comparison between data from a single 6-week nonelderly adult trial to pooled data from the two 2-week elderly trials. Furthermore, most of the comparisons were using data collected at baseline and at "discharge." The latter value was typically several days or more after the last dose that the subjects received. Additionally, the mean change in values (i.e. from baseline to treatment endpoint or using the "discharge" time-point) could not be found, except for temperature. Finally, the sponsor pooled the data of the 2 mg and 3 mg in see groups in the nonelderly trial (which is also the young age-group), even though their proposed recommended daily dose for the nonelderly is 3 mg. On the other hand, the sponsor's only recommending a 2 mg daily dose in the elderly and elderly trials did not exceed this dose level (only the data from subjects receiving this 2 mg dose level were included in the subgroup analysis).

A similar subgroup analyses was conducted on baseline, "discharge" and mean change in each vital sign parameter for ethnic and gender subgroups. Given the above caveats and

limitations regarding this type of analyses, the analyses failed to yield any remarkable subgroup differences in the mean change of any given vital sign parameter.

Subgroup analyses on baseline, "discharge" and mean change in vital sign parameters on the basis of age, gender and ethnicity are described for the double-blind phase of Study 190-049. Results were unremarkable, but the interpretation of the results is difficult due to the limitations with this type of analyses (e.g. it is not clear if "discharge" reflects a value at treatment endpoint or at some time-point after treatment, age-groups considered were only over or under 65 years old, yet only 2 subjects were $\geqslant$ 65 years old, due to the upper age-limit in eligibility criteria).

According to Section 8./10.H.14.2 of the ISS, subgroup analyses on ECG parameters on the basis of age, ethnicity or gender failed to reveal subgroup differences on treatment effects on any ECG parameter. However, ECGs were generally not obtained in the above trials until days to weeks after the last dose of study drug and in one of the 2-week elderly trials only a screening ECG assessment was conducted (no subsequent assessments, according the Schedule of Events table found in the study report).

Subgroup analyses by age, ethnicity or gender cannot be found in the ISS on descriptive statistical results of laboratory parameters or on the incidence of outliers on each parameter. Only a subgroup analyses on the incidence of categorical shifts can be found for Study 190-049.

N. Overdose Experience

Only one case of overdose of ESZ is described in the submission, which was a 24-year-old, generally healthy, female subject in the long-term Chronic Insomnia trial, Study 190-049. This subject is reported to have ingested 18 tablets from the study blister card, received upon randomization. The total amount ingested was estimated to be between 18 and 36 mg. Approximately three hours after ingestion, the patient presented to the emergency room with her friend and was described as responsive, but drowsy. She remained in the hospital, overnight for observation. Laboratory tests were negative including a negative urine drug screen. The patient was discharged in the morning with resolution of her symptoms, and without apparent sequelae.

See section O below for overdose experience with zopiclone (based on the literature and post-marketing data).

O. Experience in Pregnant and Lactating Women.

See Section P.2., below regarding experience with zopiclone. Information on ESZ in pregnant and lactating women could not be found in the submission. The sponsor proposes a Pregnancy Category B. However, the pregnancy category is determined in part by preclinical data which is under review by the Preclinical Reviewer. Other approved drugs in the same drug class as ESZ are in that Pregnancy Category C, which using the opinion of this reviewer is an appropriate category, based on the information available to this reviewer.

P. Safety Results from Other Sources

1. Post-Marketing Data:

According to the foreign marketing information provided, ESZ is not on the market in any country (see Section IVC for details).

Post marketing data on zopiclone is provided by sponsor, primarily as Periodic Safety Update Reports. All postmarketing zopiclone data provided under this NDA is under review by the Division's Safety Team. One area of primary interest in the zopiclone postmarketing database is regarding a search for any reported cases of neoplasia which is a topic currently under review by the Safety Team. However, in the opinion of this reviewer if a signal for neoplasia is not found in postmarketing, one cannot conclude that a potential association between the study drug or zopiclone and neoplasia does not exist for several reasons described in the last section of this review. Some postmarketing information is described in the next section below.

2. Literature:

This section describes the contents of Attachment II of the 3/24/03 amendment submission responding to inquiries about a review of the literature on ESZ and zopiclone, since a section on a review of the literature could not be found in the original submission. Section 8 ./10. B.1.4., is cited (in the 3/24/03 amendment submission) as the location where a review of the literature can be found in the original submission. This subsection of the review summarizes the information that was found in Section 8 .\10 .B. 1 .4. In summary the information found in this subsection appear to be a mixture of information obtained from different sources (results of the sponsor's clinical trials, results of trials on zopiclone, pharmacovigilance data or postmarketing data on zopiclone, and perhaps information from the literature, although this is not clear, as described below). Since it is not clear to him to this reviewer at what information was specifically information from a review of the literature in Section 8 .\10 .B.1 .4, the information found in this section and in subsections cited in Section 8.\10 .B. 1.4 are described below, independent of the source from which it was obtained.

In summary, the sponsor's states in the 3/24/03 amendment submission, that among 624 articles found in the worldwide literature on zopiclone, there is no reported association between this drug and "any particular rare or other serious event." During the prefiling stage of this NDA the sponsor was also asked if any signal for tumors could be found from a review of the literature. The sponsor's states in the amendment submission that "we have found no reference anywhere in the worldwide literature... of any association between tumorigenicity in man and zopiclone administration." A description of a review of the literature for ESZ cannot be found in either the amendment submission or in the original NDA submission. However, at prefiling when the sponsor was inquired about this information the sponsor responded saying that they found no articles in the literature on ESZ.

As above, the sponsor cites Section 8./10.B.1.4 as the location where a review of the literature can be found in the original submission. However, a comprehensive review of the literature of either zopiclone or ESZ cannot be found in this section. Instead, the section focuses on a description of the symptoms of insomnia, and on the efficacy trials that were conducted on ESZ to support the proposed indication. A listing of study reports is provided. This section also lists sections of the submission related to specific aspects of safety, primarily citing study reports or the ISS which describe results of clinical trials (not a review of the literature).

Subsections of Section 8./10 are also listed as providing information on the following topics (but they are not specifically described as information based on a review of the literature): drug abuse and overdose information, pregnancy and lactation, and psychiatric populations. These subsections focus on zopiclone and reference the ISS for information on ESZ (which is information from the clinical trials conducted by the sponsor) and are summarized in the

following. In the subsection on lactation and pregnancy, the sponsor indicates that treatment of ESZ or zopiclone is not recommended in pregnant or lactating patients.

Some observations with zopiclone treated patients are described (see below for further details). The subsection on psychiatric populations describes primarily open label trials and two small, placebo-controlled, crossover trials conducted on primarily internal or general medicine outpatients who had various types of psychiatric disorders or conditions. Given the study design and the patient population, these trials do not provide meaningful results relevant to the Chronic Insomnia patient population. Postmarketing data results on AEs with zopiclone are also described but do not include a section specific to the Chronic Insomnia population (includes patients with various types of psychiatric conditions or disorders).

One consistent finding in clinical trials, the literature and from postmarketing data was unpleasant or bitter taste in treated patients (which was greater in zopiclone treated patients compared to placebo treated subjects in the clinical trials).

Pharmacovigilance and postmarketing information are described in subsections that are specified by the sponsor as containing information from a review of the literature. Pharmacovigilance reports include drug abuse, mental confusion, amnesia among more frequently reported events. Periodic safety update reports are described as including reports of AEs of panic attacks with insomnia and palpitations, dependence, addiction followed by withdrawal, agitation with hallucinations, and hyponatremia "as a result of psychotic potomania."

The following summarizes additional information from subsections of 8./10.B. cited in Section 8./10.B.1.4 (these subsections were found on pages 89-99 of for clinsum.pdf file):

- The PK of zopiclone in maternal plasma and breast milk in lactating females were similar (based on results of the study and 12 lactating women).
- The effects of zopiclone on pregnancy have generally not been systematically evaluated. The sponsor describes one trial showing no differences between 40 women treated with zopiclone during the first trimester pregnancy and a matched untreated control group, except for the primary finding of a significantly lower mean birth weight and gestational age in newborns of the treated group of mothers.
- The sponsor describes postmarketing data on zopiclone regarding potential pregnancy effects. The estimated postmarketing worldwide exposure of zopiclone is [redacted] patients per year, from which the following cases were reported: four cases of fetal disorders, one case of neonatal and infancy disorder, two cases of adverse events in pregnant patients, one case of overdose, three cases of abortion and two cases of neonatal withdrawal.
- Other information on AEs in various patient populations was described, as previously summarized.

Also see the next subsection for additional information from the literature on overdose cases with zopiclone.

3. Results of Selected Trials on Zopiclone.

The following trial is being described since preclinical findings show effects of ESZ on testicular parameters and testosterone levels (based on personal communication with Preclinical Reviewer, Dr. Aisar Atrakchi). No clinical trials of ESZ were conducted to address this issue. However, the sponsor provided some information from a zopiclone trial, as follows.

Results of Study RP 27267: A Controlled Study on Sperm-Motility Effects of Zoplicone in Healthy Adults (Study RP 27267).
This study of healthy 23-43 year old men (who had conceived their own children) showed no clear effects on sperm assessments or possible trends for greater mean values on each parameter at multiple time-points during the 84-day double-blind treatment period in the 7.5 mg ESZ treatment group compared to the placebo group (N=10-11/group). These sperm parameters were volume (ml), motility (%), progressive motility (%), sperm concentration (x 1 mio./ml), and in cells with normal morphology (%). In conclusion and the results of this troll were unremarkable.

4. Overdose Experience with Zopiclone (based on data from the literature and post-marketing data).

The sponsor describes spontaneous postmarketing reports of overdose involving zopiclone. A total of 49 deaths associated with overdose were reported over a 12 year post-marketing period in which the total number of patients who were treated annually, was estimated to be 19 million patients. An additional 176 patients were reported as nonfatal overdose cases. The sponsor states that the information in most of the spontaneous reports is fragmentary and unverified. Most of the overdoses involved additional medications, and/or alcohol. Among the few patients in which plasma levels of zopiclone was known, levels ranged from 10 to 60 times greater than the expected levels at Tmax after a single dose of 7.5 mg zopiclone. The ingested dose generally ranged from 100 to 300 mg (although the ingested dose was unknown for most cases).

The major symptoms associated with nonfatal overdose involved those known to be typical of a CNS depressant. These symptoms include ataxia, mental confusion and others. Hypotonia, hypotension, respiratory and cardiovascular depression, in addition to coma were observed in severe cases. While the ingested dose was unknown for most of the cases, a dose as high as 750 mg was associated with recovery in one case.

Among 239 intentional overdoses reported in poison control center in Paris, nonfatal overdoses involved doses that ranged from 7.5 to 600 mg with the median dose of 127.5 mg. The age of individuals with reported overdose ranged from 14 to 80 years in age (mean age of 33 years, 66% were women). Coma commonly occurred at doses of 100 mg or greater.

It is not clear if there were any fatal overdoses exclusively involving zopiclone overdose and what the cause of death and the signs and symptoms leading to death were in these cases. Therefore are further clarification is needed.

Q. Conclusions on Safety Results.
Clinical trials revealed a number of CNS-related AE's and psychiatric-related AE's that are not atypical of the drug class of sedative hypnotic agents. However, the following describes observations that appeared to be atypical.

Events of Neoplasia. The most remarkable observation is the number of events of neoplasia in ESZ treated subjects compared to placebo subjects in the long-term trial Study 190-049. At least 24 events of neoplasia were reported among 593 ESZ subjects compared to no placebo subjects (out of 195 randomized subjects). Surprisingly, none of these events were reported as SAE's, yet, three events were reported as ADO's. These observations are even more striking when taking into account the stringent eligibility/screening criteria employed in this trial,

which were atypical of the trial intended to meet ICH guidelines is establishing adequate long-term safety. The stringent methods involved careful screening of subjects, that included the requirement of diagnostic tests for subjects at risk of neoplasia (including thyroid scans in subjects with active thyroid disease), as previously described. Section XI of this review addresses these observations of neoplasia in greater detail.

GU-Related Events. Another atypical finding was the number of GU related events that were reported in ESZ treated subjects compared to placebo subjects in the longer term trials in patients with Chronic Insomnia (in the 6-week study, Study 190-046 and in 6-month double-blind phase of Study 190-049, as well is in the 6-month open-label phase of this trial). The most common GU related events were breast pain, breast enlargement or engorgement, fibrocystic breast, disturbances of the menstrual cycle, uterine fibroid enlargement, and other less common GU-related events. Very few placebo treated subjects were reported to have these types of AE's. The incidence of these events reported by the sponsor a likely to be under-represented, as it was revealed that for at least some of these gender specific events the denominator used to calculate the incidence was the total number of subjects, rather than the number of subjects within the appropriate gender, as previously described. The 120-Day Update Report submission provided the incidence of AE's that may be considered AE's reflecting alterations in the reproductive endocrine system in subjects of Study 190-049. The incidence in the ESZ treated subjects during the six-month double blind phase of the study was 11.5% compared to an incidence of 4.8% in the placebo group. These events were primarily breast-related and menstrual cycle related AE's.

AEs of Infection. A drug-related and dose-dependent effect on the incidence of infections was also observed, that was reproducible in several Chronic Insomnia trials. This observation is atypical for sedative hypnotic agents. Based on the sponsor's analysis of subjects reported as having the Preferred Term AE of infection, the majority of these AE's were associated with upper-respiratory-type of AE's (reported as verbatim-term AE's). However, the sponsor's analysis of this data did not capture all subjects with infection-related AE's (other Preferred Term AEs, such as flu syndrome, viral infection, bacterial infection, or GU-related AE's of infection, or AE's that may be the result of an infectious process were not included in the analyses). Since, the total number of subjects among these other categories of AE's appears to be substantial, a conclusion that an effect of the study drug on incidence of infections is reflecting upper-respiratory/cold-like symptoms, can only be considered preliminary.

Decrease in Platelet Count and Hematuria. Another observation that was surprising was a trend for a drug-related, dose-dependent effect on platelet count in which higher dose levels (e.g. 3 mg and $\geqslant$ 3.5 mg dose-levels) showed a small mean decrease in platelet count, not observed in placebo subjects. In the longterm trial Study 190-049 ESZ subjects showed little to no change in mean platelet count over time (by monthly visits) while, placebo treated subjects showed a clear and consistent mean increase over time. Several studies also revealed a numerically greater incidence of blood in the urine (primarily in the 2-week trials in elderly Chronic Insomnia patients) and AE's of hematuria in ESZ treated subjects compared to placebo subjects.

Observations on decreased platelet and the incidence of blood in the urine appear reproducible and more marked in the Phase I trials of patients with either hepatic or renal impairment. While, the results in these special population trials could be reflecting secondary effects of hepatic or renal dysfunction on platelet count and hematuria (blood in urine upon urinalysis testing), a relationship to study drug must be considered. A potential role of the study drug must be considered, particularly since plasma levels were numerically greater with greater

degrees of hepatic or renal impairment, as shown in these trials. Based on these observations, while keeping in mind the limitations regarding the interpretation of the results, one must consider the possibility that a drug-related effect on lowering platelet count exists and may be dose-dependent. Consequently, patients receiving a dose greater than the recommended dose or patients with altered metabolism of the drug (consider alterations in CYPE1 or 3A4 metabolism), and elderly patients may be a risk of developing a low platelet count and related adverse events, such as hematuria. Yet, the observations on decreased platelet were small in magnitude in all trials described. Furthermore, results on other hematology parameters (e.g. hemoglobin, Red blood cell counts, a total white blood cell count), as well as results on the incidence of other AE's that may be associated with thrombocytopenia (GI bleed, ecchymosis, pitechea, and others) were generally unremarkable.

Hyperglycemia. Similar to the observations on platelet count and hematuria (or blood in the urine on urinalysis testing), a potential drug-related effect on glucose levels, urinary glucose and in urinary ketones as suggested by the results in elderly Chronic Insomnia patients (Study 190-047) and in the special population Phase I trials of patients with hepatic or renal dysfunction. In the 2-week elderly trial, the incidence of ESZ subjects who shifted from normal to high on glucose levels, from normal to abnormal on urinary glucose and urinary ketones was generally twice the incidence in placebo subjects. Similar observations were revealed in the two Phase I special population trials of patients with hepatic and renal impairment. As previously described one must consider that the results revealed in these special population trials are reflecting secondary effects of hepatic or renal dysfunction. An alternative secondary effect to consider, as suggested by the sponsor, may be a greater distribution of diabetics in more severely impaired study groups. However, the results in diabetics and nondiabetics were not described in the number of diabetics, and the incidence of diabetics in each study could not be found. Despite these alternative possible explanations for the study results, a potential role of ESZ must be considered, given the effects of renal and hepatic impairment on plasma levels of the study drug,. Nevertheless, treatment group differences on the incidence of abnormal shifts in glucose in urinary parameters in elderly patients were small and these observations were generally not revealed in the non-elderly Chronic insomnia trials.

One possible consideration regarding the above results on platelet count, hematuria, abnormal shifts in glucose and related urinalysis parameters is to examine results of drug-drug interaction Phase I trials. An examination of these clinical findings relative to plasma levels of the study drug, particularly in trials in which these plasma levels are manipulated, as an independent variable (as in a drug-drug interaction trial and in the hepatic and renal impairment trials), may reveal a positive relationship between plasma levels and the abnormal results on these safety parameters.

Lesions of the Oral Mucosa. Another unusual observation in the ESZ trials were reports of AE's involving lesions of the oral mucosa (stomatitis, mouth ulcer, ulcerative stomatitis and others) in the longer term trials, Study 190-046 (a 6-week trial) and in the 6-month double-blind treatment phase of Study 190-049. These events were not reported in placebo subjects of these trials. It is possible that these results are reflecting the chronic effects of dry mouth, which is a common AE associated with ESZ treatment. The AE of dry mouth is typical of the sedative hypnotic agent, as this was one of the more common AE's in zaleplon trials. However, lesions of the oral mucosa or mouth were not described in the Clinical Review of zaleplon.

Skin-Related AE's. The incidence of skin and appendage AE's was also revealed remarkable findings, in which the majority of these AE's were rash and pruritis. It is possible

that these observations are related the observations of AEs of infection which showed a drug-related and dose-dependent effect of ESZ treatment on the incidence of these AE's. However, an association between the above skin and height and related AE's and AE's of infection, is only speculative without further examination of the results and possibly further investigation.

Observations of the Incidence of CNS and Psychiatric-Related AE's. Additional AE's were observed in ESZ treated subjects as described in sections above, are not unexpected for a sedative hypnotic agent (CNS, psychiatric-related AE's, dizziness, dry mouth, somnolence, and other AE's). However, several AE's showed a greater than expected incidence in patients treated at the same dose level or at slightly higher dose-level (at 3 mg and ⩾ 3.5 mg dose-levels) than is being recommended in proposed labeling (a recommended bedtime dose of 3 mg). These included several CNS or psychiatric-related AE's such as the following:

- Memory impairment which occurred in 2.4% of ESZ treated subjects (44 out of 1839 of ITT Safety ESZ subjects) compared to 0.1% a placebo subjects (among a total of 812 ITT Safety placebo subjects) in clinical trials, combined (refer to Table VIIIC1 for enumeration of ITT Safety subjects by dose-level in each study),
- Abnormal thinking (5.5% of subjects at the ⩾3.5 mg dose-level compared to 1.5% of 3 mg ESZ subjects and 1.6% a placebo subjects)
- Confusion in 3% of 3 mg ESZ treated subjects compared to no placebo subjects in the 6-week study, Study 190-046),
- Depression in some studies (4.6% of ESZ subjects and 1.5% of placebo subjects of the 6-month double-blind treatment phase of Study 190-049)
- Agitation and/or hostility (2 SAEs, 1SAE of neurosis but exhibited "hostile behaviour," per the narrative, 5 ADOs, and several AEs) and other related AE's.

These results are contrasted to results described in the Clinical Review of zaleplon in which 0.25% of zaleplon treated subjects compared to 0.35% of zolpidem subjects in compared to 0.1% a placebo subjects in Phase II in III trials were reported to have memory impairment. In the approved labeling for zaleplon (Sonata®) abnormal thinking or confusion did not appear on the summary table of the incidence of AE's that occurred in at least 1% of zaleplon treated subjects (given 5 or 10 mg zaleplon in 28-day placebo-controlled trials). Very few to no subjects in zaleplon trials had AEs of agitation or hostility (e.g. 1/2831 zaleplon subjects reporting hostility).

While, hallucinations were reported with an incidence similar to that observed in a zaleplon trials (as described in approved labeling and in that Clinical Review of the NDA for this drug), a trial of subjects with a history of benzodiazepine abuse revealed a remarkable incidence of hallucinations. A total of 7 out of the 26 subjects had hallucinations after ESZ treatment (2 subjects after 6 mg and 5 subjects after 12 mg). 2 of these subjects had additional episodes of hallucinations at the 12 mg ESZ dose-level or during treatment with 20 mg of diazepam. Memory impairment was also reported with ESZ treatment (26 out of 28 subjects) in this 14-day, 6-way cross-over study. This AE was in only 1 S during placebo treatment and in 5 subjects during diazepam treatment compared to 13 subjects during ESZ treatment in this study. This study used 3 mg, 6 mg and 12 mg dose levels of ESZ. These results may be reflecting adverse effects of higher dose levels of ESZ (that may not susceptible to the development of tolerance) and/or may be reflecting a greater vulnerability to these AE's in this special population.

Accidental Injury AE's. The incidence of accidental injury in ESZ clinical trials also appeared to be greater in ESZ treated subjects at the 3 mg and ⩾ 3.5 mg dose-levels, than are observed with a zaleplon (in both approved labeling and in the Clinical Review of the NDA for

this drug). For example, accidental injury does not appear in the summary table of the incidence of AE's in approved labeling for zaleplon (did not make the ⩾1% criterion to be listed in the table). However, accidental injury was reported in approximately 3% of elderly Chronic Insomnia patients at the 2 mg ESZ dose-level and in approximately 7% of non-elderly Chronic Insomnia patients at the 3 mg ESZ dose-level in Phase III ESZ trials. The sponsor conducted a reanalysis of data in selected trials to determine if a relationship between CNS AE's and AEs of accidental injury could be revealed. Despite the major limitations in the interpretation of results revealed by this reanalysis, the incidence of subjects with both CNS-related and accidental injury AE's was 17% in elderly patients at the 2 mg dose-level and 20 to 30% of nonelderly patients at the 3 mg dose-level, as described in Section G.2. of this review.

Small Trends of Decreased Blood Pressure and Heart Rate. Small reproducible trends for a treatment-related and dose-dependent effect of ESZ on decreasing blood pressure and increasing heart rate was observed in several clinical trials described in previous subsection. However, these effects were small in magnitude.

Observations on Thyroid Function. Alterations in thyroid function tests (based on the incidence of outliers) and several ESZ subjects with thyroid dysfunction-related AE's (including an ADO of "thyroid disorder" with a "nodule" on the left thyroid) were revealed. However, the direction of changes in thyroid function tests was not consistent. Yet, there are several thyroid conditions, such as Hashimoto's disease, conditions associated with an inflammatory process, and other type of thyroid conditions that can results in an elevation, as well as a decrease in thyroid hormone levels and/or TSH. In the opinion of this reviewer of the trials are not adequately designed to specifically examine potential effects of the study drug on thyroid function, as suggested by the large variance in mean values and that the incidence of outliers were generally 5% or greater in placebo subjects. These findings, together with the findings on the incidence of AE's that may reflect alterations in the reproductive endocrine system suggest the need for further investigation. However, input from the Division of Metabolic and Endocrine Drug Products on these safety concerns would be appropriate. This Division has already been involved as a consultant in preparation of this NDA, as further discussed in Section XI of this review.

Additional Safety-Related Comments. Finally, while the clinical trials generally did not show any effects on liver function tests as described by the sponsor "liver damage," was reported in one ADO in Study 190-049. The information in the narrative of this subject was limited and it is not clear why this event was not classified as an SAE, given the preferred term of "liver damage." Further clarification on this event is needed.

IX. Dosing, Regimen and Administration Issues

A number of problems exist with this NDA as described elsewhere, in which the recommendation being made under Section XI is that this NDA not be approved. The discussion below describes the treatment regimen that the sponsor recommends under the Dosage and Administration section of proposed labeling.

A. Initial Treatment.

The sponsor recommends [redacted] of ESZ immediately before bedtime in adults and [redacted] before bedtime in elderly patients. The dose recommended in the sponsor's proposed labeling for patients with severe hepatic impairment is [redacted]

B. Maintenance Treatment.
Proposed labeling

X. Use in Special Populations

A. The Elderly Population

Results on efficacy, pharmacokinetics, and safety in the elderly population were described in previous sections. Previously described efficacy and safety results in elderly patients with Chronic Insomnia were results obtained from Studies 190-047 and 190-048. Pending confirmation from the OCPB Reviewer, the proposed dose of [redacted] in elderly patients is reasonable based on the pharmacokinetic results on this population. At face, the efficacy and safety results on the Studies 190-047 and 190-048 would support the recommended dose of [redacted] in this population. However, refer to the final section on conclusions and recommendations with regards to issues relevant to the interpretation of the sponsor study results.

B. Patients with Impaired Renal or Hepatic Function

Pharmacokinetic and safety results in Phase I trials conducted on patients with renal or hepatic impairment are described in previous sections of this review.

C. Male and Female Populations

No dose adjustment is recommended in proposed labeling on the basis of gender. Previous sections of this review describing study results on the basis of gender and pharmacokinetic observations.

D. Ethnic Populations

subjects were primarily Caucasian and the sample size of other ethnic subgroups was insufficient to yield meaningful or interpretable results from a subgroup analysis of safety or efficacy data.

E. Other Special Populations.

An abuse/liability trial (Study 190-016) involving patients with a history of abusing benzodiazepines is under review by the Controlled Substances Staff (CSS). This trial revealed a markedly high incidence of subjects experiencing hallucinations and/or memory impairment (reported as AE's) with ESZ treatment (if one can assume tolerance to these AEs is not exist), that may be reflecting higher doses employed in the trial and/or a potential vulnerability to these AEs. The incidence of these AEs in other patient populations treated with ESZ (non-elderly or elderly patients with Chronic Insomnia were healthy adults in other trials) was generally numerically smaller, than observed with ESZ treatment in subjects of Study 190-016.

XI. Conclusions and Recommendations

From a clinical perspective, it is recommended that this NDA submission not be approved or be given approvable status for reasons that follow.

One primary reason for recommending that this NDA not be approved is the remarkable incidence of events of neoplasia in ESZ subjects during a six-month double-blind phase of the long term trial, Study 190-049, as well as, the combined incidence with events of neoplasia

reported during the open-label phase of the trial (at least 24 events of neoplasia in the study, of which three were adverse dropouts among 593 ESZ subjects), compared to no placebo treated subjects with neoplasia (out 195 randomized subjects). Even if one uses an enumeration of at least 17 AEs based on a preferred term search for neoplasia in a line listing of AEs, 17 AEs of neoplasia is still a remarkable number (the search term used was "neop*" in a listing of AEs in Table/Listing 16.2.10 in the 190-049a.pdf file of the submission). The enumeration and a summary of these observations are discussed in more detail below. The results of Study 190-049 are even more alarming, in the opinion of this reviewer, given that the sponsor used stringent eligibility criteria/screening methods for excluding subjects with evidence of neoplasia. These criteria and screening methods are atypical for clinical drug trials, even for longterm trials. Despite these stringent screening and eligibility criteria employed a Study 190-049, the incidence of neoplasia in ESZ trials is 2 to 3 times greater than incidence observed in clinical trials of the approved drug, zaleplon, as described later in this section of the review.

Preclinical studies of zopiclone also show neoplasia, which is an issue under review by the Preclinical Reviewer. Interestingly, the types of neoplasia were multiple types (skin, breast, bladder, and others), as observed in the animal studies (lung, mammary gland, skin and others) which are under review by the Preclinical Reviewer. However, even if preclinical trials showed no evidence of neoplasia, as deemed by the Preclinical Reviewer and Team leader, the author of this Clinical review would still not recommend that this NDA be approved based on the clinical data on events of neoplasia. One concern is the potential that even if the study drug were not carcinogenic in the sense of causing neoplasia, it may be a promoter in both animals and in humans (in the opinion of the Clinical Reviewer, refer to the Preclinical Review, pending at this time regarding preclinical conclusions/recommendations). For example, it is the understanding of this Clinical reviewer that the sponsor showed that when animals are caged together a significant treatment group effect of ESZ treated animals compared to placebo is observed on the development of subcutaneous sarcoma. This effect is reportedly due to skin lesions from the animals fighting and clawing each other, since treatment group differences on this skin neoplasia are no longer observed when animals are caged separately. However, this reviewer wonders if these observations are sufficient for making this conclusion and also if an interaction effect between study drug and skin lesions in this species of animals, may exist. Furthermore, this Clinical reviewer wonders about a potential drug-effect on "fighting" behaviors, or aggression/agitation that would need to be considered and if this possibility was examined by the sponsor. However, preclinical issues are to be addressed by the Preclinical Team.

Finally, similar effective drugs are already on the market that are not known to show any evidence for or suggestive of an effect on the development and/or progression of neoplasia. Therefore, in the opinion of this reviewer, ESZ is associated with a potential risk for neoplasia that is not known to exist for drugs already on the market for treatment of insomnia (transient and/or Chronic Insomnia). The potential risk may be further magnified when considering the patient population involving a chronic illness in which patients are likely to use a sedative hypnotic agents over the long term (even if the chronic use is off-label).

The Division Safety Group is conducting a review of zopiclone safety data provided in the submission and as provided in subsequent amendment submissions. These data are primarily postmarketing data. If the Safety Group fails to find a signal for neoplasia in the postmarketing data on zopiclone, these results would not provide adequate evidence for ruling out an effect of the drug on the development or progression of neoplasia, in the opinion of this reviewer, for some of the following reasons. It is likely that neoplasia is under-reported by patients and health

professionals, particularly, once the drug is approved for the market. Postmarketing data generally reflects spontaneous reports, is generally not reliable (as the source of the information, the amount of information, among other potential confounding variables). It is unlikely that patients and health professionals would suspect a relationship between sedative hypnotic agents and neoplasia, since such a relationship is not known to exist for this drug class. Furthermore, one must consider the potential floor effect on the ability to detect a signal for neoplasia, particularly among the type of population that is represented in postmarketing data. It is difficult to interpret postmarketing data of this nature, as there are multiple confounding variables, there is no control group for comparison, and other major limitations, such as those already mentioned. Finally, even if the study drug influenced the progression of neoplasia in patients at risk, it is not likely that such a potential relationship would be a detectable signal in postmarketing data. Therefore, in the opinion of this reviewer the sponsor's postmarketing data is only useful regarding the issue of neoplasia, if a clear positive signal is revealed. A positive finding from these data would be most alarming and unusual, even for a drug that is known to be associated with development of neoplasia, due to the number of limitations in using postmarketing data to detect this type of safety signal, as already discussed.

Aside from the above described observations of neoplasia in ESZ treated patients, ESZ appears to have an atypical safety profile from the perspective of other safety findings in the clinical trials, such as a drug-related, dose-dependent effect on the incidence of infections, some evidence for GU related events associated with the study drug, unusual skin-related events, possible effects on thyroid function and others. Refer to Section VIII for further details of safety findings and conclusions.

Some of the safety observations such as GU related events and potential endocrine effects of the drug are not in the opinion of this reviewer adequately addressed in the NDA. A consult was obtained from the Division on Metabolic and Endocrine Drug Products (DMEDP) on at least two occasions before the sponsor submitted the NDA. The last time the division was consulted was during the pre-NDA phase, in which the sponsor was notified that feedback would be provided regarding the design of studies that may be considered adequate for examining potential drug effects on endocrine function. Instead of waiting for this feedback the sponsor chose to submit their NDA with the hope of conducting a trial during the review cycle. A meeting was held with the sponsor after the NDA was submitted to notify them that their clinical study proposed previously during the pre-NDA phase, was not adequate for addressing endocrine related concerns (the meeting included the Team Leader from DMEDP who conveyed this conclusion to the sponsor during this meeting). Preclinical studies showed evidence for effects on reproductive hormones and possibly the thyroid gland, but these are potential concerns under review by the Preclinical Reviewer. Some evidence for the potential for similar concerns in humans appears to exist from the safety data described in this review. In the opinion of the author of the Clinical Review, further input from DMEDP on the need for further investigation is needed. However, since it is recommended this NDA not be given an approvable or approved status, input from DMEDP would not be relevant (unless at the Agency level, the NDA was given an approvable status).

Additional Clinical issues with this NDA and reasons for not recommending that the NDA be approved are discussed in a subsection below. However, this review does not discuss potential or existing preclinical, CMC, and biometric issues (such as issues discussed in Section II regarding the need for DMFs for certain formulations, preclinical concerns, among others), as these issues and others (including potential OCPB issues) are currently under review by each

respective reviewer at the time of this writing (refer to their final reviews, once they are completed for their conclusions and recommendations). Finally, a DSI review is pending at the time of this writing.

The Enumeration and Summary of Results on AE's of Neoplasia.
This subsection discusses the breakdown, enumeration and summary of events of neoplasia. A large number of events of neoplasia were reported in the long-term trial, Study 190-049 which was the only trial with ESZ treatment exceeding six weeks (the next longest trial was Study 190-046 which was a 6-week trial). The large number of these events is even more remarkable when considering the multiple, stringent screening methods and eligibility criteria in subjects with active thyroid disease and in subjects at risk or with a history of neoplasia, as previously described. These screening methods and eligibility criteria are atypical of the long-term trial conducted to establish adequate long-term safety of a study drug (conducted to meet ICH guidelines for an NDA submission).

During the six-month double-blind phase of the trial a total of **18 events of neoplasia** (3 ADOs and 15 AEs of which 2 were specifically indicated as benign skin neoplasia) were reported among a total of 593 ITT Safety subjects in the ESZ group (18/593 subjects; 3 %). None of the placebo subjects out of a total of 195 subjects in the placebo group (ITT Safety) had reported events of neoplasia. An additional event of "nodule" on the left thyroid was also reported as an adverse dropout in an ESZ subject. Events of neoplasia were also reported during the open 6-month, open-label 3 mg ESZ days of the trial. The total of 7 **events of neoplasia** was reported in this phase of the study of which two events were specifically designated as benign skin neoplasia and one was listed as a suspicious Papinicolau (Pap) smear (not listed as neoplasia) . These 7 additional events brings the **grand total of events of neoplasia** reported in ESZ subjects (given the 3 mg bedtime dose recommended in proposed labeling) to **24 (not counting the ADO of thyroid "nodule" and AE of suspicious Pap smear)** during this 12-month, long-term trial, compared to no placebo subjects with neoplasia during 6-month double-blind phase of the trial. The types of neoplasia reported during the 6-month double-blind phase of the trial were as follows (with a number of reported events, of which 3 were reported as ADOs and others as AEs): 2 hepatic neoplasia, 3 breast neoplasia, 6 unspecified neoplasia, 1 prostate neoplasia, 1 mouth neoplasia, 3 skin carcinomas, and 2 benign skin neoplasia. Additionally ADO of thyroid "nodule" was reported. The types of neoplasia reported in the open-label phase of the trial were as follows (with the number of reported events for each AE term/type of neoplasia): 2 benign skin neoplasia, 2 bladder neoplasia, 1 suspicious pap smear (not reported as neoplasia, but considered by this reviewer as neoplasia, given lack of information), 1 cervix neoplasia, and 1 breast neoplasia.

Using Adobe Acrobat word stem search tool and using "neop*" as the search term multiple hits were revealed in primarily Tables 16.2.10 and 16.2.12 of the 190-049a.pdf file in the original submission. A total of 17 subjects with neoplasia were found in the former table (a line listing of AEs by subject identification numbers for Study 190-049). It is not clear which of these AEs match to previously described AEs (based on summary tables on the incidence of AEs or other tables as described in detail in Section VIII). Some of these AEs in the line listing had reported terms such as the following for some of the AEs, some of which were vague, while others suggest benign events: mole irritation on back, lipoma, nasal polyps, lump on palate, nevi on back, abnormal prostate biopsy, gastric and sigmoid polyps, among others. Even if some of

these AEs may be benign, the basis for reported terms in most cases is not clear or specified (e.g. no narrative description including signs, symptoms, diagnostic tests, etc could not be found). For example a description of any biopsy results of events involving gastrointestinal polyps and bladder polyps in another subject are not included in line listings of AEs.

It is not clear why the enumeration of neoplasia using information from other tables in the submission (the total of at least 24 events) do not match with the enumeration of AEs in the AE line listing table 16.2.10. The total of at least 24 events was based on data from other tables, found in the submission, as described in Section VIII of this review and summarized above. The search using "neop*" as a search term would not capture all potential or probable neoplasia (e.g. nodules, suspicious pap smear, carcinoma among others). It is noted that the 3 ADOs of neoplasia listed in Table 16.2.12 are among the 17 AEs listed in Table 16.1.10 which may account for possible redundancy of 3 events of neoplasia reported as AEs in summary tables of AEs, but this does account for other discrepancies between the enumeration of events described in each of two previous paragraphs (at least 24 events versus 17 events). Finally, at least one additional AE of neoplasia that was not described above was revealed from the neop* search. A post-treatment neoplasia listed in Table 16.2.9.2 in the 190-049a.pdf file of the submission was uterine neoplasm (reported term of uterine mass) which could be drug-related.

It is not clear to this reviewer why the sponsor did not report all events of neoplasia as SAE's. It also does not appear to this reviewer that the reported AE's of neoplasia during the double-blind phase of the trial were redundant to AE's reported during the open-label phase of the trial, since the summary tables were clearly indicated as the incidence of AE's in each of the phases of these trials. Furthermore, AE's reported in the open-label phase of the trial were mostly neoplasia of a different type (suspicious pap smear, cervix neoplasia, breast and bladder neoplasia) and were fewer in the number of subjects with neoplasia, then reported during the double-blind phase of the trial. Therefore, redundancy between treatment emergent AEs of neoplasia reported during the open-label phase and the double-blind phase does not appear to explain the above discrepancies on the total number of reported AEs in the trial.

Multiple types of tumors were found in animal studies with zopiclone, as previously described in this review. The above clinical results are highly suspicious of a drug-related effect on development or progression of neoplasia.

One subject was found to have multiple tumors in Study 190-049 which is highly suggestive that this subject had pre-existing and undiagnosed neoplasia prior to treatment. However, one must also consider the possibility of a drug-related progression of neoplasia or drug-related conversion from benign to malignant neoplasia, as suggested by the following. She had a normal mammogram and Pap smear within approximately one year prior to study entry. Upon imaging at screening she had breast tumors (also found on previous imaging, perhaps referring to the mammogram in the previous year, but not specifically states). These tumors were <u>not</u> considered to be consistent of malignancy and were <u>diagnosed as benign</u>. Furthermore, one tumor was found to have "resolved" compared to earlier films (presumably the mammogram in the previous year). After approximately six months on the study drug she was found upon imaging to have multiple tumors (breast, lung, liver, and kidney) and was reported as an SAE of hepatic neoplasia. Refer to the copy of the narrative provided in this review in Section VIII for further details.

Enumeration of AEs of Neoplasia in Clinical Trials of Zaleplon for Comparison. The above results are contrasted with results described in a review with dated 7/14/98 on zaleplon

(Sonata®), conducted by Dr. Paul Andreason (who is currently Team Leader) in which a total of 8 SAE's of neoplasia were reported during the development program for this drug out of a total of 3726 zaleplon treated subjects (of which at least 400 subjects received up to six months and 53 subjects received up to 12 months of study drug according to summary tables in the review approximately 730 zaleplon subjects were in ongoing trials of 6-12 months in duration). The type of neoplasia reported in these 8 subjects were as follows: 1 breast neoplasia, 2 GI neoplasia, 3 skin neoplasia, 1 unspecified neoplasia, 1 lung neoplasia, and 1 uterine neoplasia. It is not clear how many of the eight zaleplon subjects with SAE's of neoplasia were in long-term trials, since the enumeration of subjects above is for all zaleplon trials, combined. Based on this reviewer's experience, one would not expect the zaleplon trials to include the stringent criteria for screening subjects for neoplasia that was employed in the long-term trial, Study 190-049 on ESZ.

Additional Issues regarding the Submission. The above observations are reasons for recommending that this NDA not be approved (and not be given approvable status). This subsection describes additional problems that exist with the submission and are also reasons for recommending that the NDA not be approved. Perhaps some of these problems could be resolved upon further clarification and/or more complete information from the sponsor, but this would not appear to be the case for all problems described below.

One major problem with the submission is regarding the quality, completeness and accuracy of the information provided in the submission, which are in the opinion of this reviewer, are not adequate. Perhaps the most remarkable observation regarding this concern is the following. A number of events of "neoplasia" or "neoplasm" were found in tables that were End-of-Text tables in Study 190-049 or in tables in a separate attachment to the study report, such as tables in the an attachment, the 190-049a.pdf file). These events included not only AE's but also several adverse dropouts of neoplasia that were reported. Furthermore, none of these events were classified by the sponsor is SAE's or described in summary sections of SAEs. A discussion on these events of neoplasia could not be found in the ISS (or another sections of the submission, such as the Study Report for Study 190-049), despite the Divisions expressed concerns of preclinical observations of neoplasia and given the history
The stringent screening, eligibility criteria relevant to neoplasia for Study 190-049 are also surprising and atypical of a trial of this nature (the only longterm ESZ trial conducted and had the primary purpose of demonstrating adequate safety). Finally, these eligibility criteria were not listed among the Inclusion and Exclusion criteria section of the study report, but instead were found under the section describing screening procedures.

The following are additional problems or concerns that in the opinion of this reviewer impacts on the quality of several studies and the interpretation of the data and results:

- A number of protocol deviations were found in various trials that involved what this reviewer considers as serious errors in the conduct of the studies, such as the following:
    a) Placebo subjects "inadvertently" received a stock solution of active study drug (a clear statement on the exact concentration and volume of the stock solution that was given to these subjects cannot be found, or a description off the consequences regarding safety could not be found)
    b) A few subjects participated in a given study twice at two separate study sites (it is not clear how this occurred)

c) Given the multiple problems described in Section V of the review on "Data Quality and Completeness" and in other sections of this review, and the scope of the problems, together with the overall recommendation that this NDA not be approved, CRFs were not compared to narratives (such a comparison is an additional method for testing or spot checking for accuracy and consistency of the information in the submission).
d) A number of errors were revealed in various study reports with some revisions provided by the sponsor, after the original submission, as discussed in this review (for example one study report was submitted months after the original submission in which the sponsor reported that they inadvertently left out information PSG data which they subsequently provided).
e) Also see next item.

- In some trials (e.g. Study 190-026) a committee classified subjects as "important" protocol deviators (although the protocol already had prespecified the definition of protocol violators). The data from these subjects was excluded from the primary statistical analyses on primary and key secondary efficacy variables. It appears to other trials also employed this method for determining "evaluable" subjects from which the data would be used for primary efficacy analyses. This is an issue that requires further clarification (e.g. which trials employed these methods, a clear definition for "evaluable" subjects and "important protocol violators" and methods for identifying these subjects and for how subjects were selected for inclusion in efficacy results, why and how sponsor chose which data to include in primary versus secondary efficacy analyses). These issues impact on the quality of the data, the statistical methods being employed in the trials, and in turn, the interpretability of the efficacy results.
- The study drug was associated with an unpleasant taste as observed in single-dose and multiple dose trials, including Phase III trials with an incidence of up to approximately one third of ESZ treated subjects in a given trial. This effect on the incidence of unpleasant taste was dose-dependent (and efficacy results suggested a potential dose-dependent effect, based on the results as provided by the sponsor). Furthermore, this AE involved a substantial proportion of subjects within the proposed therapeutic dose-level. Refer to Section VI and VII for details and the concern that the placebo was not adequately matched in taste to the ESZ tablet or oral solution, impacting on the quality of the study and interpretability of study results (i.e. due to an inadequate double-blind study design).
- Clinstat\insomnia\190-049\190-049.pdf on p.64: describes a blinded interim analysis that was "performed and planned, but is not included in this report because it was superceded by the planned unblinded analysis." The following is also described: "NDA submission had been scheduled to occur prior to database lock and treatment unblinding, but a delay in the NDA timing made it possible to complete the unblinded analysis in time for inclusion in the NDA". Also in other sections of each study report are a number of protocol amendments, some that include statistical changes and some changes made after data unblinding and after the database lock. These changes are not addressed in this review, given the overall recommendation that the NDA not be given an approvable or approved status. Several statistical protocol changes are biometric-related issues.
- A number of problems with the ISS and safety information were also described in previous sections of this review that impact on the interpretability of safety results (e.g.

little to no information on orthostatic vital sign measures, time-points employed for many safety measures which were often when plasma levels would be at trough or days after drug exposure, the incidence of gender specific events need to be calculated using the gender appropriate number of subjects within the given gender, among other problems with the safety data).

Because of the multiple problems the above only addresses some of the major problems or concerns and does not describe other aspects of the submission regarding the efficacy results and results on studies focusing on safety related issues specific to the drug class (e.g. results of studies examining tolerance, withdrawal or rebound effects, respiratory drive and other potential effects that are known for the drug class of sedative hypnotic agents). Other questions or areas needing further clarification are not addressed in the above, but are mentioned in previous sections of this review. A listing of some additional areas (but is not a complete listing) is also provided in Attachment 1.

/S/

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
HFD 120/
P Andreason
K Brugge
M Mille
T Laughren
A Atkrachi
A Jackson
G Gill-Sangha
N Khin

APPENDIX

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Table VI.B 1. List of Investigators for 190-045

Site No. Investigator Center	Site No. Investigator Center
0169 Bruce Corser, M.D. Subinvestigators:	0177 Gary Zammit, Ph.D. Subinvestigators:
0170 Milton K. Erman, M.D. Subinvestigators:	0186 James Wellman, M.D. Subinvestigators:
0174 Martin Scharf, Ph.D. Subinvestigators:	0227 Andrew Jamieson, M.D. Subinvestigators:
0176 James Walsh, Ph.D Subinvestigators:	

Table VI.B 2. List of Investigators for study 190-049 (continued on the next page)

Site No. Investigator Center	Site No. Investigator Center
0087 Thomas Fiel, D.O. Tempe Primary Care Associates, PC 5030 South Mill Ave. D-12 Tempe, AZ 85282	0392 Louise Beckett, M.D. IPS Research Company 1211 N. Shartel Suite 407 Oklahoma City, OK 73103
0088 Harry I. Geisberg, M.D. Radiant Research 1118 Cornelia Road Anderson, SC 29621	0393 David Berwald, M.D. Radiant Research, Inc. – St. Louis 12401 Olive Blvd., Ste. 103 St. Louis, MO 63141
0093 Ernie Riffer, M.D. Central Phoenix Medical Clinic, LLC 4747 North 7th Street, Suite 100 Phoenix, AZ 85014	0396 Nancy G. Campbell, M.D. Breco Research, Inc 902 Frostwood, Suite 223 Houston, TX 77024
0110 Patrick A. Finnegan, M.D. Longmont Medical Research 1925 West Mountain View Ave. Longmont, CO 80501	0397 Patricia Coleman, M.D. PCM Medical Services, P.C. 1601 E. Michigan Avenue Lansing, MI 48912
0218 Howard L. Offenberg, M.D. Radiant Research, Gainesville Gainesville Clinical Research Center 1014 NW 57th Street, Suite A, C, & D Gainesville, FL 32605	0398 Lydia G. Corn, M.D. ICSL – Clinical Studies 5969 Cattleridge Blvd, Suite 100 Sarasota, FL 34232
0256 Stuart J. Simon, M.D., M.D., FCCP Southeast Research associates 2550 Windy Hill Road Suite 301 Marietta, GA 30067	0400 Seymour Diamond, M.D. Diamond Headache Clinic 467 West Deming Place, Ste. 500 Chicago, IL 60614
0317 William Jennings, M.D. (Robert B. Nett, Jr., M.D., RPh, original PI) San Antonio Center for Clinical Research 8122 Datapoint Drive, Suite 1010 San Antonio, TX 78229	0401 John Docherty, M.D. Comprehensive NeuroScience, Inc. 21 Bloomingdale Road White Plains, NY 10605
0349 Margarita Nunez, M.D. ICSL-Clinical Studies 780-94th Avenue North Suite 102 St Petersburg, FL 33702	0405 Raul E. Gaona, Sr., M.D. Pro Research Group, LLC 98 Briggs, San Antonio, TX 78224
0391 Danny R. Bartel, M.D. North Texas Neurology Research 1722 Ninth Street Wichita Falls, TX 76301	0406 Edward Gillie, M.D. ICSL – Clinical Studies 12751 New Brittany Blvd, Suite 501 Ft Myers, FL 33907
	0407 Lawrence D. Ginsberg, M.D. Red Oak Psychiatry Associates, PA 17115 Red Oak Drive, Ste. 109 Houston, TX 77090

Table VI.B 2. List of Investigators for study 190-049, continued (also continued on next page)

Site No. Investigator Center	Site No. Investigator Center
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0410 Randall Grimshaw, M.D. Cycle Solutions, Inc 1101 Capitol of Texas Highway, South Bldg. G, Suite 257 Austin, TX 78746	0425 Linda Murray, DO Radiant Research, Inc 6677-13th Avenue North, Suite 3B St Petersburg, FL 33710
0412 James L. Heaton, M.D. Blairsville Family Practice 637 Deep South Farm Road Blairsville, GA 30512	0427 Richard G. Pellegrino, M.D., PhD Central Arkansas Research One Mercy Lane, Suite 502 Hot Springs, AR 71913
0413 James R. Herron, M.D. Herron Medical Center, Ltd. 1150 N. State Street Chicago, IL 60610	0428 Patrick H. Peters, Jr., M.D. Texas Medical Research Associates 6547 Bandera San Antonio, TX 78238
0415 Rakesh Jain, M.D. R/D Clinical Research, Inc 461 This Way P.O. Drawer B Lake Jackson, TX 77566	0429 Bryan C. Pogue, M.D. Radiant Research Boise 6565 W. Emerald Street, Boise, ID 83704
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0417 Gregory Bishop, M.D. (Christopher Kelsey, M.D., original PI) Innovations in Behavioral Health 3969 Fourth Avenue, Ste. 203 San Diego, CA 92103 San Diego Center for Research 3969 Fourth Avenue, Ste. 203 San Diego, CA 92103	0431 Dennis S. Riff, M.D. Advanced Clinical Research Institute 1211 W. La Palma Avenue, Suite 602, 302, 306 Anaheim, CA 92801
0418 Keith Klatt, M.D. Radiant Research 5331 SW Macadam Ave., Ste. 210 Portland, OR 97201	0432 Sid Rosenblatt, M.D., FACP 16259 Laguna Canyon Road Irvine, CA 92618
0420 Michael T. Levy, M.D. 450 Seaview Avenue Staten Island, NY 10305	0433 John Rubino, M.D. Multi-Specialty Research Assoc. of NC 3509 Haworth Drive, Suite 100 Raleigh, NC 27609
0421 Benjamin F. Lewis, M.D. Piedmont Clinical Research 100 West Main Street Ninety Six, SC 29666	0434 Gladstone Sellers, M.D. Southeast Research Associates 2550 Windy Hill Road Suite 301 Marietta, GA 30067
	0438 Danny H. Sugimoto, M.D. Cedar-Crosse Research Center 800 S. Wells Street Suite M-15, Chicago, IL 60607

Table VI.B 2. List of Investigators for study 190-049, continued (also continued on next page)

Site No. Investigator Center	Site No. Investigator Center
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0442 Mark A. Wentworth, M.D. 12702 Toepperwein, Ste. 120 San Antonio, TX 78233	0454 John E. Ervin, M.D. The Center for Pharmaceutical Research 1010 Carondelet Drive, Ste 220/224 Kansas City, MO 64114
0443 Gerald D. Wolfley, M.D. Radiant Research, Inc 7555 E. Osborn, Suite 200 Scottsdale, AZ 85251	0455 W. Thomas Garland, M.D. FACC Radiant Research – Lawrenceville 3100 Princeton Pike, Bldg 1, 3rd Floor Lawrenceville, NJ 08648
0444 Laurence G. Yellen, M.D. Cardiology Associates 5555 Reservoir Drive, Suite 209 San Diego, CA 92120	0456 Suzanne K. Gazda, M.D. Neurology Clinic of San Antonio 4410 Medical Drive Suite 540 San Antonio, TX 78229
0445 Donald Anderson, M.D. Affiliated Research Institute 11374 Mountain View Avenue Loma Linda, CA 92354	0457 E. Walter Hood, M.D. ICSL Clinical Studies 6065 Roswell Road, Suite 820 Atlanta, GA 30328
0446 Luis E. Angles, M.D. Heart of America Research Institute 5799 Broadmoor, Suite 138 Mission, KS 66202	0458 Richard P. Hull, M.D. North Alabama Neuroscience Research Associates 1104 Monroe Street Huntsville, AL 35801
0447 Mira Baron, M.D. Rapid Medical Research, Inc. 29001 Cedar Road, Suite 202 Cleveland, OH 44124	0459 Alan J. Kivitz, M.D. Altoona Center for Clinical Research 1125 Old Route 220 North Duncansville, PA 16635
0448 Marshall Block, M.D. Radiant Research – Phoenix 407 West Osborn Phoenix, AZ 85013	0460 William S. Mullican, M.D. MediSphere Medical Research Center,LLC 1401 Professional Blvd., Suite 100 Evansville, IN 47714
0450 Michael DePriest, M.D. Las Vegas Center for Clinical Research 6039 Eldora Avenue, Ste. H Las Vegas, NV 89146	0461 Michael J. Noss, M.D. Radiant Research, Inc. 7720 Montgomery Road Cincinnati, OH 45236
0451 Steven M. Eisen, M.D. ICSL – Clinical Studies 400 Market Street, Ste. 425 Philadelphia, PA 19106	0462 Ana Y. Perez, M.D. Pro-Research Group, LLC 343 W. Houston Suite 702 San Antonio, TX 78205

Table VI.B 2. List of Investigators for study 190-049, continued

Site No. Investigator Center	Site No. Investigator Center
0463 Adrian Jaffer, M.D. (Robert T. Reid, M.D., original PI) Allergy & Rheumatology Medical Clinic,Inc. 9850 Genesee Avenue, Suite 860 La Jolla, CA 92037-1233 0464 Michele Reynolds, M.D. Radiant Research – Dallas North 7515 Greenville, Suite 801 Dallas, TX 75231 0465 Douglas R. Schumacher, M.D. Radiant Research-Columbus 1275 Oletangy River Road, Suite 202 Columbus, OH 43212 0466 Jeffrey S. Simon, M.D. Northbrooke Research Center 9275 North 49th Street, Suite 200 Brown Deer, WI 53223	0467 Kenneth J. Weiss, M.D. Delaware Valley Research Associates, Inc 922 Fayette Street Conshohocken, PA 19428 0470 Diane Normandin, M.D. (Isabelle Desjardins, M.D., original PI) Clinical Research of West Florida 2147 NE Coachman Road Clearwater, FL 33765 0471 Walter S. Dunbar, M.D. Medical Dietics, Inc 4300 Paces Ferry Road, Suite 359 Atlanta, GA 30339 0472 Dennis C. McCluskey, M.D. Radiant Research 754 S. Cleveland Avenue, Suite #200 Mogadore, Ohio 44260 0473 Jeffrey Geohas, M.D. Chicago Center for Clinical Research 515 North State St., Ste. 2700 Chicago, IL 60610

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Table VI.B 3. List of Investigators for study 190-026 (also continued on next page)

Site No. Investigator Center	Site No. Investigator Center
168 Jed Black, M.D. Subinvestigators:	172 Russell Rosenberg, Ph.D. Subinvestigators:
Human Sleep Lab 780 Welch Road #203 Palo Alto, CA 94304 169 Bruce Corser, M.D. Subinvestigators:	
Cincinnati Regional Sleep Center 2123 Auburn Avenue, Suites 322, 341 Cincinnati, OH 45219 170 Milton K. Erman, M.D. Subinvestigators:	Northside Hospital Sleep Medicine Institute 5780 Peachtree Dunwoody Road Suite 120 Atlanta, GA 30342 173 Thomas Roth, Ph.D. Subinvestigators:
Denise M. Williams-Jones, CCRC Pacific Sleep Medicine Services, Inc. 9834 Genesee Ave, Suite 328 La Jolla, CA 92037 171 Andrew Jamieson, M.D. Subinvestigators:	Henry Ford Hospital Sleep Disorders and Research Center 2799 West Grand Blvd., CFP-3 Detroit, MI 48202 174 Martin B. Scharf, Ph.D. Subinvestigators:
Sleep Medicine/Research Dept. Presbyterian Hospital of Dallas 8200 Walnut Hill Ln. Jackson Bldg. Ground Level Dallas, TX 75231	Tri-State Sleep Disorders Center 1275 East Kemper Road Cincinnati, OH 45246 175 Jonathan Schwartz, M.D. Subinvestigators:
	Sleep Disorders Center of Oklahoma 4401 S. Western Oklahoma City, AK 73109

Table VI.B 3. List of Investigators for study 190-026, continued

Site No. Investigator Center	Site No. Investigator Center
180 Marvin Eugene Vollmer, M.D. Subinvestigators: Community Hospital East 1500 N. Ritter Ave. Indianapolis, IN 46219 182 Arthur R. Knodel M.D. Subinvestigators: St. Clare Hospital 11315 Bridgeport Way SW Tacoma, WA 98499 183 Carl Rosenberg, M.D. Subinvestigators: University Hospitals of Cleveland Division of Clinical Research Departments of Neurology & Medicine Lakeside Building 5512 11,100 Euclid Ave. Cleveland, OH 44106 184 R. Bart Sangal, M.D. Subinvestigators: Clinical Neurophysiology Services, P.C. 44199 Dequindre #311 Troy, MI 48098	185 Renata Shafor, M.D. Subinvestigators: None San Diego Sleep Disorders Center 1842 Third Avenue San Diego, CA 92101 186 James J. Wellman, M.D. Subinvestigators: The Sleep Research Lab 1970 Cliff Valley Way Suite 101 Atlanta, GA 30329 187 J. Catesby Ware, Ph.D. Subinvestigators: Sleep Disorders Center Eastern Virginia Medical School/Sentara Norfolk General Hospital 600 Gresham Drive Norfolk, VA 23507

Table VI. B. 4. Study 190-026: Subject Disposition in a "Pivotal" Transient Insomnia Efficacy, Parallel Group Trial in Healthy Adults.

A total of 436 subjects were randomized to treatment, as follows:

- Placebo: 98 subjects;
- Esopiclone 1.0 mg: 47 subjects;
- Esopiclone 2.0 mg: 97 subjects;
- Esopiclone 3.0 mg: 98 subjects;
- Esopiclone 3.5 mg: 96 subjects.

Only one subject discontinued; one (1.0%) placebo-treated subject left during the study visit because of a family emergency (Reference: EOT Table 1.1.1).

Table VI. B. 5. Study 190-045: Subjects Disposition in a 6-Way Cross-over 2-Night PSG Adult Chronic Insomnia Study.

Subject Disposition	N (%)
Randomized*	65
Completed	63 (96.9%)
Discontinued	2 (3.1%)
Voluntary withdrawal	1 (1.5%)
Protocol violation	1 (1.5%)
***Subjects were randomized to one of six treatment sequences in this 6-way cross-over his study.**	

Table VI. B. 6. Study 190-046: Subject to Disposition in a 6-Week . "Pivotal" Adult Outpatient Chronic Insomnia Trial.

Subject Disposition	Placebo n (%)	Esopiclone 2.0 mg n (%)	Esopiclone 3.0 mg n (%)
Randomized	99 (100.0)	104 (100.0)	105 (100.0)
Completed	94 (94.9)	97 (93.3)	101 (96.2)
Discontinued	5 (5.1)	7 (6.7)	4 (3.8)
AE	0 (0.0)	3 (2.9)	0 (0.0)
Protocol violation	2 (2.0)	2 (1.9)	0 (0.0)
Voluntary withdrawal	2 (2.0)	2 (1.9)	2 (1.9)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Treatment failure	0 (0.0)	0 (0.0)	0 (0.0)
Did not meet entry criteria	0 (0.0)	0 (0.0)	1 (1.0)
Other	1 (1.0)	0 (0.0)	1 (1.0)

Reference: EOT Table 1.1.2

Table VI.B.7. Study 190-047: Subject Disposition in a 2-week "Pivotal" PSG-Efficacy Trial in Elderly Patients.*

Disposition	Placebo n (%)	Esopiclone 1.5 mg n (%)	Esopiclone 2.0 mg n (%)	Total n (%)
Randomized	128	28	136	292
Completed	122 (95.3)	28 (100.0)	133 (97.8)	283 (96.9)
Discontinued	6 (4.7)	0 (0.0)	3 (2.2)	9 (3.1)
AE	3 (2.3)	0 (0.0)	2 (1.5)	5 (1.7)
Protocol violation	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Voluntary withdrawal	2 (1.6)	0 (0.0)	0 (0.0)	2 (0.7)
Did not meet entry criteria	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)

Note: Percentages are calculated from subjects randomized.

***Two subjects received of double-blind treatment twice (i.e. participated in this study at two different sites) as described in this review.**

Table VI. B. 8. Study 190-048: Subject Disposition in a 2-week "Pivotal" PSG-Efficacy Trial in Elderly Patients.*

Disposition	Placebo n (%)	Esopiclone 1.0 mg n (%)	Esopiclone 2.0 mg n (%)	Total n (%)
Randomized	81	74	79	234
Randomized and dosed	80	72	79	231*
Completed	73 (91.3)	67 (93.1)	70 (88.6)	210 (90.9)
Discontinued	7 (8.8)	5 (6.9)	9 (11.4)	21 (9.1)
AE	5 (6.3)	1 (1.4)	2 (2.5)	8 (3.5)
Voluntary withdrawal	2 (2.5)	2 (2.8)	7 (8.9)	11 (4.8)
Did not meet entry criteria	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.4)
Other	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.4)

* Three subjects were randomized but discontinued from the study before receiving any study medication (see below for details).

Note: Percentages are calculated from subjects randomized and dosed.

Reference: Table 14.1.1, Appendix 16.2.1.

Table VI. B. 9. Study 190-049: Subject Disposition in a Long-term Trial on Adult Outpatient with Chronic Insomnia.

Subject Disposition	DOUBLE-BLIND PERIOD (MONTHS 1-6)		OPEN-LABEL PERIOD (MONTHS 7-12)
	Placebo n (%)	Esopiclone 3.0 mg n (%)	Esopiclone 3.0 mg n (%)
Randomized	196 --	595 --	-- --
Received treatment	195 (100)	593 (100)	471 (100)
Completed 6 months of treatment	111 (57)	360 (61)	382 (81)
Discontinued	84 (43)	233 (39)	89 (19)
AE	14 (7)	76 (13)	18 (4)
Protocol violation	7 (4)	17 (3)	9 (2)
Voluntary withdrawal	50 (26)	81 (14)	35 (7)
Lost to follow-up	8 (4)	52 (9)	15 (3)
Did not meet entry criteria	1 (1)	0 (0)	0 (0)
Other	4 (2)	7 (1)	12 (3)

Note: Percentages are based on subjects who received treatment. Only those reasons for discontinuation that actually occurred have been displayed. Subjects 420004 and 460010, who were randomized to esopiclone 3.0 mg and placebo, respectively, voluntarily withdrew prior to the first dose of study drug; Subject 439034, who was randomized to esopiclone 3.0 mg, was discontinued for Other reasons prior to the first dose.

Reference: EOT Table 1.1.5.

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Table VI. B. 10. Demographic Features of the ITT Population in Study 190-045 on Non-Elderly Chronic Insomnia Patients

Characteristic	Statistic	Treatment Sequence*						All Subjects (N=65)
		ACBEFD (N=8)	BDCFAE (N=12)	CEDABF (N=10)	DFEBCA (N=11)	EAFCDB (N=12)	FBADEC (N=12)	
Age (years)	N	8	12	10	11	12	12	65
	Mean	40.5	42.8	41.2	40.2	41.3	37.5	40.6
	SD	7.9	7.6	8.8	8.5	14.1	10.0	9.7
	Median	40.5	43.5	40.0	38.0	37.0	37.5	38.0
	Min, Max	31, 52	32, 55	27, 55	24, 56	22, 63	24, 55	22, 63
Race								
Caucasian	n (%)	5 (62.5)	10 (83.3)	3 (30.0)	10 (90.9)	8 (66.7)	8 (66.7)	44 (67.7)
Black	n (%)	2 (25.0)	1 (8.3)	3 (30.0)	1 (9.1)	3 (25.0)	3 (25.0)	13 (20.0)
Asian	n (%)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (8.3)	3 (4.6)
Hispanic	n (%)	1 (12.5)	1 (8.3)	2 (20.0)	0 (0.0)	1 (8.3)	0 (0.0)	5 (7.7)
Gender								
Female	n (%)	7 (87.5)	11 (91.7)	7 (70.0)	9 (81.8)	8 (66.7)	6 (50.0)	48 (73.8)
Male	n (%)	1 (12.5)	1 (8.3)	3 (30.0)	2 (18.2)	4 (33.3)	6 (50.0)	17 (26.2)
Height (cm)	N	8	12	10	11	12	12	65
	Mean	162.4	167.9	165.0	165.6	165.6	171.1	166.6
	SD	9.3	8.0	11.9	7.1	10.9	9.5	9.6
	Median	163.8	165.7	165.1	165.1	162.6	174.6	165.1
	Min, Max	147, 177	160, 189	145, 183	155, 179	152, 188	152, 183	145, 189
Weight (kg)	N	8	12	10	11	12	12	65
	Mean	70.7	72.4	66.3	74.3	79.9	75.0	73.4
	SD	13.9	16.5	16.7	19.5	19.0	11.3	16.4
	Median	76.9	66.5	66.0	68.9	74.8	78.2	72.6
	Min, Max	52, 84	52, 106	45, 100	55, 118	51, 106	54, 92	45, 118
BMI (kg/m^2)	N	8	12	10	11	12	12	65
	Mean	26.7	25.7	24.1	27.0	29.0	25.6	26.4
	SD	4.5	5.5	3.9	6.6	6.0	3.1	5.1
	Median	25.6	24.1	23.5	24.9	29.6	25.5	25.3
	Min, Max	19, 33	19, 38	17, 32	19, 42	20, 40	20, 32	17, 42

*Treatment sequence: A = placebo; B = esopiclone 1.0 mg; C = esopiclone 2.0 mg; D = esopiclone 2.5 mg; E = esopiclone 3.0 mg; F = 10.0 mg zolpidem.

Reference: Table 14.1.3.

Table VI. B. 11. Demographic Features of the ITT Population in Study 190-046, Non-Elderly Chronic Insomnia Patients

Characteristic	Statistic	Placebo (n=99)	Esopiclone 2.0 mg (n=104)	Esopiclone 3.0 mg (n=105)	All Subjects (N=308)	P-value[1]
Age (years)	N	99	104	105	308	0.1094
	Mean (SD)	40.8 (11.8)	40.6 (11.5)	38.0 (11.7)	39.8 (11.7)	
	Median	41.0	40.0	37.0	39.0	
	Min, Max	21, 64	21, 63	21, 63	21, 64	
Race						0.6833
Caucasian	n (%)	63 (63.6)	69 (66.3)	72 (68.6)	204 (66.2)	
Black	n (%)	18 (18.2)	19 (18.3)	14 (13.3)	51 (16.6)	
Asian	n (%)	3 (3.0)	3 (2.9)	3 (2.9)	9 (2.9)	
Hispanic	n (%)	13 (13.1)	11 (10.6)	16 (15.2)	40 (13.0)	
Other	n (%)	2 (2.0)	2 (1.9)	0 (0.0)	4 (1.3)	
Gender						0.0325
Male	n (%)	43 (43.4)	38 (36.5)	28 (26.7)	109 (35.4)	
Female	n (%)	56 (56.6)	66 (63.5)	77 (73.3)	199 (64.6)	
Height (cm) – male	N	43	37	28	108	0.2317
	Mean (SD)	178.5 (5.9)	177.1 (7.0)	175.7 (8.4)	177.3 (7.0)	
	Median	180.3	177.8	179.1	178.4	
	Min, Max	165, 189	157, 196	152, 185	152, 196	
Height (cm) – female	N	56	66	76	198	0.5299
	Mean (SD)	163.5 (7.6)	164.6 (7.4)	164.9 (6.9)	164.4 (7.3)	
	Median	165.1	165.1	165.1	165.1	
	Min, Max	144, 180	137, 179	137, 183	137, 183	
Weight (kg) – male	N	43	37	28	108	0.7282
	Mean (SD)	83.2 (13.4)	85.9 (13.3)	84.8 (14.0)	84.5 (13.4)	
	Median	80.7	85.4	82.6	83.9	
	Min, Max	64, 125	58, 124	59, 116	58, 125	
Weight (kg) – female	N	56	66	76	198	0.1041
	Mean (SD)	69.7 (14.0)	77.0 (23.2)	73.2 (17.2)	73.5 (18.8)	
	Median	67.5	68.9	70.3	68.7	
	Min, Max	45, 113	45, 168	44, 133	44, 168	
BMI (kg/m^2)	N	99	103	104	306	0.0498
	Mean (SD)	26.1 (4.5)	28.0 (6.7)	27.1 (6.1)	27.1 (5.9)	
	Median	25.3	26.8	26.3	25.9	
	Min, Max	19, 42	19, 57	18, 50	18, 57	

[1]Continuous variables were analyzed using an ANOVA model with effects for treatment and site. Categorical variables were analyzed using the Cochran-Mantel-Haenzel test for general association controlling for site.

Reference: Table 14.1.3.

Table VI. B. 12. Demographic Features of the ITT Population in the Double-blind Phase of Study 190-049, Non-Elderly Chronic Insomnia Patients

Characteristic	Statistic	Placebo (n=195)	Esopiclone (n=593)	All Subjects (N=788)	P-value[1]
Age (years)	n	195	593	788	0.2380
	Mean (SD)	43.2 (11.1)	44.3 (11.4)	44.1 (11.4)	
	Median	44.0	45.0	45.0	
	Min, Max	21, 65	21, 69	21, 69	
Race					0.2874
Caucasian	n (%)	153 (78.5)	469 (79.1)	622 (78.9)	
Black	n (%)	27 (13.8)	77 (13.0)	104 (13.2)	
Asian	n (%)	5 (2.6)	5 (0.8)	10 (1.3)	
Hispanic	n (%)	10 (5.1)	38 (6.4)	48 (6.1)	
Other	n (%)	0 (0.0)	4 (0.7)	4 (0.5)	
Gender					0.7526
Male	n (%)	70 (35.9)	220 (37.1)	290 (36.8)	
Female	n (%)	125 (64.1)	373 (62.9)	498 (63.2)	
Height (cm)	n	195	590	785	0.2132
	Mean (SD)	168.1 (9.7)	169.0 (9.6)	168.8 (9.6)	
	Median	167.3	167.6	167.6	
	Min, Max	145, 193	137, 196	137, 196	
Weight (kg)	n	195	591	786	0.0027
	Mean (SD)	79.1 (21.8)	84.5 (22.2)	83.2 (22.2)	
	Median	75.8	81.6	80.2	
	Min, Max	42, 171	37, 168	37, 171	
BMI (kg/m^2)	n	195	589	784	0.0039
	Mean (SD)	27.8 (6.5)	29.5 (7.2)	29.1 (7.1)	
	Median	26.5	28.1	27.8	
	Min, Max	15, 49	17, 59	15, 59	

[1]Continuous variables were analyzed using an ANOVA model with effects for treatment and site. Categorical variables were analyzed using the Cochran-Mantel-Haenzel test for general association controlling for site.

Note: This table summarizes data for Population A + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Reference: Table 14.1.3A.

Table VI. B. 13. Demographic Features of the ITT Population in the Open Label-Phase of Study 190-049, Non-Elderly Chronic Insomnia Patients

Characteristic	Statistic	Open-label Esopiclone 3 mg (n=471)	Previous Double-Blind Treatment	
			Placebo (n=111)	Esopiclone 3 mg (N=360)
Age (years)	n	471	111	360
	Mean (SD)	45.6 (11.0)	45.1 (11.0)	45.7 (11.1)
	Median	46.0	45.0	46.5
	Min, Max	21, 65	21, 65	21, 64
Race				
Caucasian	n (%)	379 (80.5)	88 (79.3)	291 (80.8)
Black	n (%)	59 (12.5)	14 (12.6)	45 (12.5)
Asian	n (%)	7 (1.5)	3 (2.7)	4 (1.1)
Hispanic	n (%)	24 (5.1)	6 (5.4)	18 (5.0)
Other	n (%)	2 (0.4)	0 (0.0)	2 (0.6)
Gender				
Male	n (%)	176 (37.4)	37 (33.3)	139 (38.6)
Female	n (%)	295 (62.6)	74 (66.7)	221 (61.4)
Height (cm)	n	470	111	359
	Mean (SD)	168.5 (9.7)	166.4 (9.6)	169.2 (9.7)
	Median	167.6	165.1	167.6
	Min, Max	145, 196	145, 193	147, 196
Weight (kg)	n	471	111	360
	Mean (SD)	82.4 (22.3)	76.3 (21.0)	84.3 (22.4)
	Median	78.9	72.6	82.1
	Min, Max	37, 170	44, 141	37, 170
BMI (kg/m^2)	n	470	111	359
	Mean (SD)	28.9 (7.1)	27.4 (6.5)	29.4 (7.2)
	Median	27.6	26.0	28.1
	Min, Max	16, 58	16, 48	17, 58

Note: This table summarizes data for Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Reference: Table 14.1.2B.

Table VI. B. 14. Demographic Features of the ITT Population in Study 190-047 Elderly Chronic Insomnia Patients

Characteristic		Statistic	Placebo (n=128)	Esopiclone 1.5 mg (n=28)	Esopiclone 2.0 mg (n=136)	P-value [1]
Age (years)		N	128	28	136	0.2826
		Mean (SD)	70.7 (4.9)	71.4 (5.1)	71.5 (5.2)	
		Median	70.0	70.5	71.0	
		Min, Max	64, 85	65, 81	64, 86	
Race	Caucasian	n (%)	116 (90.6)	27 (96.4)	120 (88.2)	0.9595
	Black	n (%)	8 (6.3)	1 (3.6)	11 (8.1)	
	Asian	n (%)	1 (0.8)	0 (0.0)	1 (0.7)	
	Hispanic	n (%)	3 (2.3)	0 (0.0)	4 (2.9)	
Gender	Male	n (%)	37 (28.9)	11 (39.3)	49 (36.0)	0.5102
	Female	n (%)	91 (71.1)	17 (60.7)	87 (64.0)	
Height (cm) – male		N	37	11	49	0.3236
		Mean (SD)	175.5 (7.4)	174.7 (7.6)	174.6 (8.1)	
		Median	177.8	172.7	176.5	
		Min, Max	155, 188	163, 188	150, 191	
Height (cm) – female		N	91	17	87	0.8929
		Mean (SD)	161.8 (6.7)	161.1 (4.6)	161.7 (6.5)	
		Median	162.1	161.3	162.6	
		Min, Max	147, 180	152, 170	144, 174	
Weight (kg) - male		N	37	11	49	0.6271
		Mean (SD)	82.9 (12.5)	85.2 (16.0)	81.3 (12.2)	
		Median	79.8	88.5	81.2	
		Min, Max	64, 116	59, 119	57, 117	
Weight (kg) - female		N	91	17	86	0.2062
		Mean (SD)	68.4 (13.5)	71.4 (10.4)	70.7 (12.0)	
		Median	65.7	71.7	67.6	
		Min, Max	44, 117	49, 93	42, 102	
BMI (kg/m^2)		N	128	28	135	0.2185
		Mean (SD)	26.3 (4.2)	27.7 (4.3)	26.9 (4.0)	
		Median	25.7	27.6	26.3	
		Min, Max	18, 39	20, 37	16, 38	

1. Continuous variables were analyzed using an ANOVA model with effects for treatment and site. Categorical variables were analyzed using the Cochran-Mantel-Haenzel test for general association controlling for site. Only the placebo and esopiclone 2.0 mg groups were included in the analyses.

Reference: Table 14.1.3.

Table VI. B. 15. Demographic Features of the ITT Population in Study 190-048 of Elderly Patients with Chronic Insomnia.

Characteristic	Statistic	Placebo (n=80)	Esopiclone 1.0 mg (n=72)	Esopiclone 2.0 mg (n=79)	All Subjects (N=231)	P-value[1]
Age (years)	N	80	72	79	231	0.7373
	Mean (SD)	72.0 (5.0)	72.7 (4.5)	72.2 (5.3)	72.3 (4.9)	
	Median	72.0	72.0	72.0	72.0	
	Min, Max	64, 83	65, 82	64, 85	64, 85	
Race						0.2840
Caucasian	n (%)	75 (93.8)	69 (95.8)	79 (100.0)	223 (96.5)	
Black	n (%)	3 (3.8)	2 (2.8)	0 (0.0)	5 (2.2)	
Hispanic	n (%)	2 (2.5)	1 (1.4)	0 (0.0)	3 (1.3)	
Gender						0.6764
Male	n (%)	31 (38.8)	31 (43.1)	36 (45.5)	98 (42.4)	
Female	n (%)	49 (61.3)	41 (56.9)	43 (54.4)	133 (57.6)	
Height (cm) – male	N	31	31	35	97	0.6226
	Mean (SD)	177.0 (7.3)	174.8 (7.0)	175.6 (8.1)	175.8 (7.5)	
	Median	176.5	175.3	177.8	176.0	
	Min, Max	157, 189	160, 185	160, 188	157, 189	
Height (cm) - female	N	47	40	41	128	0.9952
	Mean (SD)	162.0 (6.1)	161.7 (5.6)	161.7 (6.7)	161.8 (6.1)	
	Median	162.6	162.6	160.0	162.6	
	Min, Max	147, 174	150, 175	150, 178	147, 178	
Weight (kg) – male	N	31	31	36	98	0.6969
	Mean (SD)	88.1 (17.2)	84.8 (13.3)	84.2 (13.8)	85.6 (14.7)	
	Median	84.8	82.1	82.6	83.1	
	Min, Max	56, 145	60, 110	61, 125	56, 145	
Weight (kg) – female	N	49	41	43	133	0.4803
	Mean (SD)	69.1 (15.3)	70.2 (12.5)	67.2 (10.7)	68.8 (13.0)	
	Median	64.0	71.2	65.3	67.4	
	Min, Max	49, 116	49, 111	49, 90	49, 116	
BMI (kg/m^2)	N	78	71	75	224	0.5054
	Mean (SD)	27.0 (5.0)	27.2 (4.5)	26.3 (3.7)	26.8 (4.4)	
	Median	26.1	26.7	26.3	26.5	
	Min, Max	18, 43	19, 42	20, 41	18, 43	

[1]Continuous variables were analyzed using an ANOVA model with effects for treatment and site. Categorical variables were analyzed using the Cochran-Mantel-Haenzel test for general association controlling for site.

Reference: Table 14.1.3.

Table VI. B.16. Demographic Features of the ITT Population in Study 190-026

Parameter	Placebo (n=98)		(S)-Zopiclone 1.0 mg (n=47)		(S)-Zopiclone 2.0 mg (n=97)		(S)-Zopiclone 3.0 mg (n=98)		(S)-Zopiclone 3.5 mg (n=96)	
Age (years); mean (SD)	32.6	(6.8)	33.6	(7.0)	35.4	(7.7)	33.2	(6.9)	33.8	(8.1)
Gender										
Male; n (%)	40	(40.8)	24	(51.1)	37	(38.1)	49	(50.0)	37	(38.5)
Female; n (%)	58	(59.2)	23	(48.9)	60	(61.9)	49	(50.0)	59	(61.5)
Race										
Caucasian; n (%)	75	(76.5)	34	(72.3)	77	(79.4)	77	(78.6)	79	(82.3)
Black; n (%)	15	(15.3)	10	(21.3)	17	(17.5)	15	(15.3)	14	(14.6)
Asian; n (%)	3	(3.1)	2	(4.3)	2	(2.1)	2	(2.0)	1	(1.0)
Hispanic; n (%)	5	(5.1)	1	(2.1)	0	(0.0)	4	(4.1)	1	(1.0)
Other; n (%)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	1	(1.0)
Height (cm)										
Males; mean (SD)	176.9	(6.9)	181.1	(6.7)	180.8	(6.3)	180.1	(6.4)	180.1	(6.4)
Females; mean (SD)	165.6	(7.1)	164.1	(8.2)	166.5	(6.7)	163.7	(6.4)	166.0	(5.6)
Weight (kg)										
Males; mean (SD)	80.5	(10.0)	82.2	(12.0)	83.8	(11.8)	84.1	(12.6)	84.1	(9.6)
Females; mean (SD)	64.9	(9.3)	65.1	(9.4)	65.0	(10.2)	63.1	(8.1)	66.1	(11.2)
BMI; mean (SD) kg/m^2	24.5	(3.0)	24.6	(3.1)	24.3	(3.4)	24.7	(3.5)	24.7	(3.5)

Reference: Table 14.1.3.1.

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Table VIC.1. Study 190-045 Schedule of Assessments

Observation and Procedure	Pre-Screen	Screening	Dosing[1]			End-of-Study[5]
	Visit 1		Visits 2, 3, 4, 5, 6, 7			Visit 8
Timing	**-18 to -8 days**	**-8 to -1 days**	**Pre-dosing**	**Post-dosing**	**Washout 3-7 days**	**5-7 days from last dose**
Telephone prescreen questionnaire	X					
Sleep diary	X					
Informed Consent	X					
Inclusion/Exclusion Criteria	X		X			
Medical History/ Sleep History/Psychiatric History	X					
12-lead ECG	X					X
Vital Signs	X		X	X		X
Physical Examination including Brief Neurological Exam	X					X
Romberg Test	X	X		X		
Heel-to-Toe Gait Test	X	X		X		
Clinical Laboratory Tests	X					X
Hepatitis B & C Test	X					
Urine Drug Screen	X	X[4]	X[4]			
Serum Pregnancy Test	X					X
Urine Pregnancy Test		X[4]	X[4]			
Adverse experiences	X	X	X	X	X	X
Concomitant Medications	X	X	X		X	X
PSG Recording[1]		X[2]		X		
Morning Questionnaire		X		X		
Evening Questionnaire		X	X			
POMS questionnaire		X	X			
Medical Events Calendar	X	X	X	X	X	X

1. PSG recording start time was based on median bedtime ± 30 minutes as calculated from the sleep diary. The Evening Questionnaire and POMS were completed prior to PSG recording start. The Morning Questionnaire was completed each morning after PSG recording was complete.
2. Single-blind placebo was administered prior to all screening PSGs.
3. Each dosing visit was two nights. Subjects were discharged each morning after completing all evaluations. The washout period between each dosing was 3-7 days. There was no washout period after Visit 7; instead, all subjects returned for an end-of-study visit 5-7 days after the last Visit 7 dose.
4. Obtained at first screening PSG and on Day 1 of each Visit.
5. Completed within 5-7 days after last dose. All randomized subjects who prematurely discontinued completed this visit at the time of discontinuation.

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Table VIC2. "Next Day Effects" Parameters in Study 190-045.

- Morning sleepiness (mm): Measured by a visual analog scale with the Morning Questionnaire, where 0 mm = "very sleepy" and 100 mm = "not at all sleepy".
- Daytime alertness (mm): Measured a visual analog scale with the Evening Questionnaire, where 0 mm = "very sleepy" and 100 mm = "wide awake and alert".
- Daily ability to function (mm): Measured by a visual analog scale with the Evening Questionnaire, where 0 mm = "poor" and 100 mm = "excellent".
- POMS: Mood states included six categories called mood factors (i.e., factors) with each factor receiving a score based on subject's scoring of individual items (i.e., adjectives). Factors included tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The adjectives that were presented to the subjects and their corresponding factor are presented in Table 9.5.1.3.1-1.

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Table VIC3. Objective PSG Efficacy Measures in Study 190-045

Sleep induction, sleep duration, and sleep maintenance parameters

- Latency to persistent sleep (LPS; minutes): time from lights out to the first of 20 consecutive epochs (10 minutes) of non-wake, as determined by PSG recordings.
- Sleep efficiency: (total sleep time)/(total recording time) x 100. For this endpoint, total sleep time was defined as the number of non-wake epochs from the beginning of recording to the end of recording divided by 2. If total recording time was greater than 960 epochs (480 minutes), total sleep time was calculated from the PSG truncated at 480 minutes.
- Wake time after sleep onset (WASO; minutes): The number of wake epochs after the onset of persistent sleep to the end of the recording, divided by 2.
- Number of awakenings: The number of times, after onset of persistent sleep, that there was a wake entry of at least one-minute duration. Each awakening must have been separated by an epoch of non rapid eye movement (NREM) sleep stage 2, 3/4, or rapid eye movement (REM) sleep.
- Wake time before persistent sleep (minutes): The number of wake epochs that occurred before the onset of persistent sleep divided by 2.
- Wake time during sleep (minutes): The number of wake epochs after the onset of persistent sleep prior to the last NREM sleep stage 2, 3/4, or REM sleep, divided by 2.
- Wake time after sleep (minutes): The number of wake epochs from the last NREM sleep stage 2, 3/4, or REM sleep to the end of the recording, divided by two. If there were no NREM sleep stages 2, 3/4, or REM sleep, wake time after sleep included all wake epochs after onset of persistent sleep divided by 2. The end of recording was considered to be at 480 minutes (960 epochs) if more epochs were present.

Sleep architecture parameters

- Percent of total sleep time in NREM sleep stage 1: (sleep time in NREM sleep stage 1)/(total sleep time) x 100.
- Percent of total sleep time in NREM sleep stage 2: (sleep time in NREM sleep stage 2)/(total sleep time) x 100.
- Percent of total sleep time in NREM sleep stage 3/4: (sleep time in NREM sleep stage 3/4)/(total sleep time) x 100.
- Percent of total sleep time in REM sleep: (REM sleep time)/(total sleep time) x 100.
- Total time in NREM sleep stage 1: Minutes of sleep.
- Total time in NREM sleep stage 2: Minutes of sleep.
- Total time in NREM sleep stage 3/4: Minutes of sleep.
- Total time in REM sleep: Minutes of sleep.

Table VIC4. Subjective Efficacy Measures in Study 190-045 (from the Morning Questionnaire)

- Sleep latency (minutes): Time after lights-out until sleep.
- Total sleep time: Minutes of sleep.
- Number of awakenings: Number of times awake during sleep.
- Wake time after sleep onset: Minutes awake after sleep onset, before awakening for the day.
- Quality of sleep: Measured by a visual analog scale where 0 mm = "poor" and 100 mm = "excellent".
- Depth of sleep: Measured by a visual analog scale where 0 mm = "very light" and 100 mm = "very deep".

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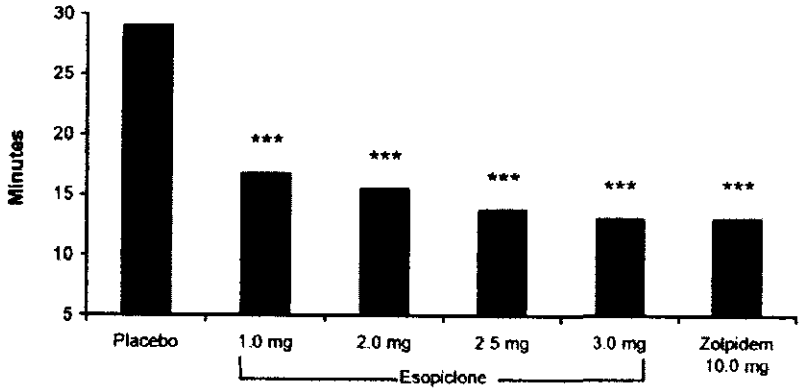
Figure VIC1 A-C. Study 190-045 Efficacy Results (ITT Population).

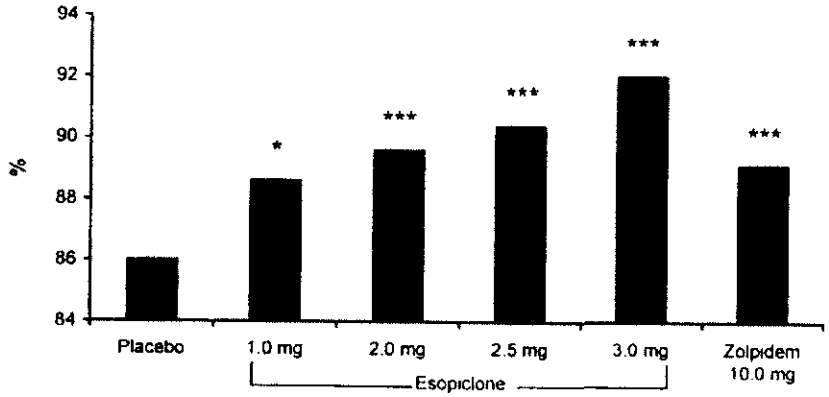
Panel A. Primary Efficacy Variable: Median Objective LPS



***p≤0.0001. The pairwise comparison with placebo used the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

Reference: Table 14.2.1.

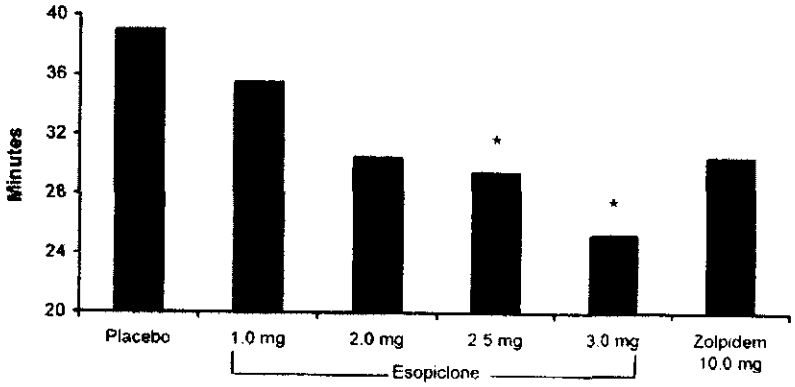
Panel B. "Key" Secondary Efficacy Variable: Median Objective Sleep Efficiency



*p≤0.05; ***p≤0.0001. The pairwise comparison with placebo used the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

Reference: Table 14.2.2.

Panel C. Another "Key" Secondary Efficacy Variable: Median Objective WASO



*p≤0.05. The pairwise comparison with placebo used the appropriate contrast from an ANOVA model on rank-transformed data wit treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

Reference: Table 14.2.3.

Table VIC5 Panels A-C. Study 190-045 Efficacy Results (ITT Population).

A. Primary Efficacy Variable: Median Objective LPS

Objective Latency to Persistent Sleep (minutes)	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	63	63	63	65	64	64
Mean	37.8	25.2	20.1	18.6	18.3	16.6
SD	31.1	24.1	17.6	18.7	19.6	14.4
Median	29.0	16.8	15.5	13.8	13.1	13.1
Min, Max						
Overall treatment effect[1]			≤0.0001			
Pairwise p-value vs. placebo[2]		≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

[1]The overall treatment effect was tested using an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect. The analysis compared the three highest esopiclone dose groups combined (2.0, 2.5, and 3.0 mg) with the placebo group using the ANOVA model with the contrast between the three esopiclone groups combined and the placebo group.

[2]The pairwise comparison used the appropriate contrast from the same ANOVA model.

B. "Key" Secondary Efficacy Variable: Median Objective Sleep Efficiency

Objective Sleep Efficiency (%)	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	63	63	63	65	64	64
Mean	83.9	86.8	88.9	89.7	89.2	88.8
SD	8.8	7.1	7.0	6.4	8.1	6.3
Median	86.0	88.6	89.6	90.4	92.0	89.1
Min, Max						
Overall treatment effect[1]			≤0.0001			
Pairwise p-value vs. placebo[2]		0.0065	≤0.0001	≤0.0001	≤0.0001	≤0.0001

[1]The overall treatment effect was tested using an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect. The analysis compared the three highest esopiclone dose groups combined (2.0, 2.5, and 3.0 mg) with the placebo group using the ANOVA model with the contrast between the three esopiclone groups combined and the placebo group.

[2]The pairwise comparison used the appropriate contrast from the same ANOVA model.

C. Another "Key" Secondary Efficacy Variable: Median Objective WASO

Objective Wake Time After Sleep Onset (minutes)	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	63	63	63	65	64	64
Mean	43.1	41.4	36.0	33.1	35.9	39.3
SD	32.5	26.5	25.0	23.2	31.7	28.5
Median	39.0	35.5	30.5	29.5	25.3	30.5
Min, Max						
Overall treatment effect[1]			0.0086			
Pairwise p-value vs. placebo[2]		0.9977	0.1104	0.0184	0.0122	0.3287

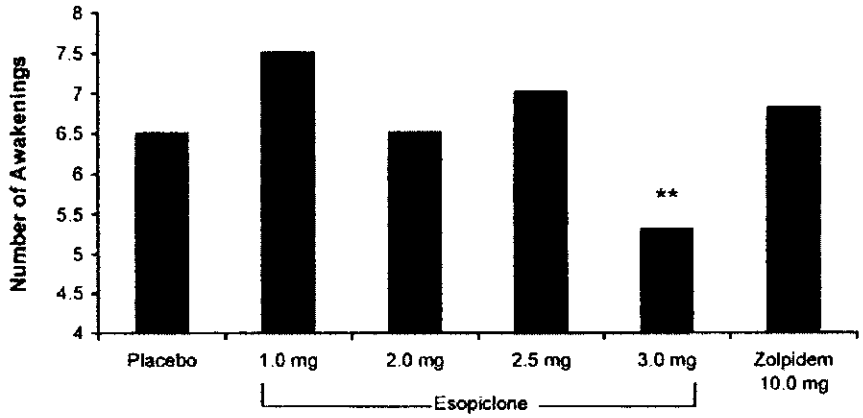
[1]The overall treatment effect was tested using an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect. The analysis compared the three highest esopiclone dose groups combined (2.0, 2.5, and 3.0 mg) with the placebo group using the ANOVA model with the contrast between the three esopiclone groups combined and the placebo group.

[2]The pairwise comparison used the appropriate contrast from the same ANOVA model.

Reference Table 14.2.3.

Figure VIC2 and Table VIC6 Study 190-045 Results on an Additional Secondary Variable: Median Objective Number of Awakenings (ITT Population).

Figure VIC2.



**p≤0.01. The pairwise comparison with placebo used the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

Table VIC6.

Objective Number of Awakenings	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	63	63	63	65	64	64
Mean	7.7	7.8	7.6	7.1	6.5	7.2
SD	4.1	3.5	4.5	4.4	4.4	4.3
Median	6.5	7.5	6.5	7.0	5.3	6.8
Min, Max						
Pairwise p-value vs. placebo[1]		0.4795	0.5983	0.1587	0.0031	0.1838

[1]The pairwise comparison used the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

Table VIC7 Study 190-045 Results on Additional Secondary Variables (Objective and Subjective Measures).

Efficacy Measure	Placebo[a] (n=63)	Esopiclone[a] 1.0 mg (n=63)	Esopiclone[a] 2.0 mg (n=63)	Esopiclone[a] 2.5 mg (n=65)	Esopiclone[a] 3.0 mg (n=64)	Zolpidem 10.0 mg[a] (n=64)
Additional Objective Measures						
Wake Time Before Persistent Sleep (min)	27.0	13.8***	12.0***	10.3***	10.8***	9.3***
Wake Time During Sleep (min)	30.8	28.0	26.0	25.3*	23.3**	27.4
Wake Time After Sleep (min)	0.3	0.5	0.0	0.3	0.5	0.3
Subjective Measures						
Sleep Latency (min)	47.5	27.5***	25.0***	25.0***	25.0***	25.0***
Total Sleep Time (min)	375.0	382.5	412.5***	420.0***	420.0***	411.3***
Number of Awakenings	3.5	3.0	3.0**	3.0*	2.5***	2.5**
Wake Time After Sleep Onset (min)	42.5	35.0	27.5**	25.0**	28.8***	30.0*
Quality of Sleep[b]	43.5	47.0*	58.0***	55.0**	62.0***	56.0***
Depth of Sleep[c]	40.3	46.0*	56.5***	53.0***	59.5***	56.5***

*0.01<p≤0.05; **0.0001<p≤0.01; ***p≤0.0001. The pairwise comparison was performed using the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

[a]All values represent group medians.

[b]Measured by a visual analog scale, where 0 mm = "poor" and 100 mm = "excellent".

[c]Measured by a visual analog scale, where 0 mm = "very light" and 100 mm = "very deep".

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Table VIC8 Panels A-C. Study 190-045 Results on "Next Day Effects" Subjective Measures (ITT Population)

A. Subjective Morning Sleepiness

Morning Sleepiness (mm)[1]	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	62	62	63	64	63	63
Mean	39.8	43.8	44.6	44.7	45.4	43.5
SD	20.1	22.0	21.3	19.9	22.8	20.4
Median	36.8	42.3	42.0	45.3	44.5	43.3
Min, Max						
Pairwise p-value vs. placebo[2]		0.1842	0.0670	0.0416	0.0307	0.1257

[1]Measurements are based on a 100 mm visual analog scale from the Morning Questionnaire, where 0 mm = "very sleepy" and 100 mm = "not at all sleepy".

[2]The pairwise comparison was performed using the appropriate contrast from an ANOVA model with treatment, sequence, and visit as fixed effects, and subject nested within sequence as a random effect.

B. Subjective Daytime Alertness

Daytime Alertness (mm)[1]	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	61	63	62	65	63	64
Mean	47.0	52.5	55.2	50.7	52.2	55.8
SD	24.1	24.6	24.3	25.6	27.5	27.7
Median	40.0	57.0	56.5	50.0	56.0	62.5
Min, Max						
Pairwise p-value vs. placebo[2]		0.0968	0.0094	0.2731	0.0567	0.0012

[1]Measurements are based on a 100 mm visual analog scale from the Evening Questionnaire, where 0 mm = "very sleepy" and 100 mm = "wide awake and alert".

[2]The pairwise comparison was performed using the appropriate contrast from an ANCOVA model with treatment, sequence, and visit as fixed effects, subject nested within sequence as a random effect, and the pre-dose assessment as a covariate.

Note: All values refer to post-dose measurements.

C. Subjective Daytime Ability to Function

Daytime Ability to Function (mm)[1]	Placebo (n=63)	Esopiclone 1.0 mg (n=63)	Esopiclone 2.0 mg (N=63)	Esopiclone 2.5 mg (N=65)	Esopiclone 3.0 mg (n=64)	Zolpidem 10.0 mg (n=64)
N	61	63	62	65	63	64
Mean	52.2	58.7	59.5	54.1	56.6	56.2
SD	22.9	21.9	22.4	23.8	26.2	26.4
Median	50.0	58.0	59.0	51.0	60.0	53.0
Min, Max						
Pairwise p-value vs. placebo[2]		0.0134	0.0046	0.4606	0.0424	0.0494

[1]Measurements are based on a 100 mm visual analog scale from the Evening Questionnaire, where 0 mm = "poor" and 100 mm = "excellent".

[2]The pairwise comparison was performed using the appropriate contrast from an ANCOVA model with treatment, sequence, and visit as fixed effects, subject nested within sequence as a random effect, and the pre-dose assessment as a covariate.

Note: All values refer to post-dose measurements.

Table VIC9 Panel A-B. Sleep Architecture Results of Each Non-Elderly Adult PSG Trial of Patients with Chronic Insomnia, Studies 190-045 (A) and 190-046 (B), Respectively.

Panel A. Study 190-045.

Sleep Architecture Measure	Placebo[a] (n=63)	Esopiclone[a] 1.0 mg (n=63)	Esopiclone[a] 2.0 mg (n=63)	Esopiclone[a] 2.5 mg (n=65)	Esopiclone[a] 3.0 mg (n=64)	Zolpidem 10.0 mg[a] (n=64)
% Total Sleep Time in NREM Stage 1	10.0	9.8	9.2	9.1	9.1*	8.7*
% Total Sleep Time in NREM Stage 2	57.5	58.6	59.4*	60.9**	61.1**	58.4
% Total Sleep Time in NREM Stage 3/4	11.1	11.2	10.1	11.7	10.4	13.0
% Total Sleep Time in REM	19.9	20.1	19.0	18.7*	18.2*	18.5
Total Time in NREM Stage 1 (min)	40.0	39.0	40.3	38.8	38.6	38.4
Total Time in NREM Stage 2 (min)	234.3	244.5**	259.0***	257.8***	261.0***	248.5***
Total Time in NREM Stage 3/4 (min)	43.8	48.3	42.3	51.5	45.5	53.1**
Total Time in REM (min)	81.5	82.5	79.5	80.3	80.9	78.0

*0.01<p≤0.05; **0.0001<p≤0.01; ***p≤0.0001. The pairwise comparison was performed using the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect.

[a]All values represent group medians.

References: Tables 14.2.5.1-14.2.5.4, and 14.2.5.5-14.2.5.8.

Panel B. Study 190-046.

Sleep Architecture Measure	Placebo (n=99)	Esopiclone 2.0 mg (n=104)	Esopiclone 3.0 mg (n=105)
% Total Sleep Time in NREM Stage 1	10.3	9.3	9.2
% Total Sleep Time in NREM Stage 2	56.5	58.7	59.3*
% Total Sleep Time in NREM Stage 3/4	11.5	12.1	12.9
% Total Sleep Time in REM	20.4	19.2*	18.2**
Total Time in NREM Stage 1 (min)	39.9	38.9	39.3
Total Time in NREM Stage 2 (min)	219.0	244.0**	252.0**
Total Time in NREM Stage 3/4 (min)	46.1	51.3	52.5
Total Time in REM (min)	84.5	77.8	77.5

*0.01<p≤0.05; **p≤0.01. The pairwise comparison was performed using the appropriate contrast from an ANOVA model on rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure. All values represent group medians.

References: Tables 14.2.5.1, 14.2.5.2, 14.2.5.3, 14.2.5.4, 14.2.5.5, 14.2.5.6, 14.2.5.7, 14.2.5.8.

Table VIC10. Schedule of Assessments in Study 190-046 (4-6 Week PSG Trial in Non-elderly Chronic Insomnia Patients).

Observation and Procedure	Pre-Screen	Screening								End-of-study
Visit	1			2		4	5	6		7[6]
Timing		-20 to -10 days	-10 to -1 days	Baseline BI	Day 1	Day 15	Day 29	Day 43 and 44	Rebound BI and 2	5-7 days post last dose
Telephone Pre-Screen Questionnaire	X	X								
Sleep Diary	X	X								
Informed Consent		X								
Inclusion/Exclusion Criteria			X							
Medical History/ Sleep History/Psychiatric History		X	X							
Physical Examination including Brief Neurological Exam		X								X
12-lead ECG		X								X
Vital Signs		X	X	X	X	X	X		X	X
Romberg Test			X[1,3]	X[1,3]	X[1,3]	X[1,3]	X[1,3]		X[1,3]	
Heel-to-Toe Gait Test			X[1,3]	X[1,3]	X[1,3]	X[1,3]	X[1,3]		X[1,3]	
Clinical Laboratory Tests		X							X[1,3]	X
Hepatitis B & C Test		X								
Menstrual History/Hormonal Therapy		X							X	X
Urine Drug Screen		X	X[4]	X[4]		X[4]	X[4]			
Serum Pregnancy Test		X								X
Urine Pregnancy Test			X[4]	X[4]		X[4]	X[4]			
Adverse Events		X	X	X	X	X	X		X	X
Concomitant Medications		X	X	X	X	X	X		X	X
Study Medication			X[3]	X[3]	X	X	X		X[3]	
PSG Recording[1]			X	X	X	X	X		X	
Morning Questionnaire			X[3,1]	X[3,1]	X[3,1]	X[3,1]	X[3,1]	X[3,1]	X[3,1]	
Evening Questionnaire[2]			X[3,1]	X[3,1]	X[3,1]	X[3,1]	X[3,1]		X[3,1]	
DSST			X[3,1]	X[3,1]	X[3,1]	X[3,1]	X[3,1]		X[3,1]	
POMS Questionnaire			X[3,1]	X[3,1]	X[3,1]	X[3,1]	X[3,1]		X[3,1]	
Medical Events Calendar (MEC)		X	X	X	X	X	X		X	X

1. PSG recording start time is based on median bedtime ± 30 minutes as calculated from sleep diary. 2. Completed at home Days 2-14, 16-28, and 30-44. 3. Dosed with single-blind placebo
4. Obtained at first screening PSG AND on first night of each Visit 5. Obtained blood sample for thyroid function test and 17β-estradiol in morning after Rebound 1
6. Completed 5-7 day after last dose. All randomized subjects who prematurely discontinued completed this visit at the time of discontinuation

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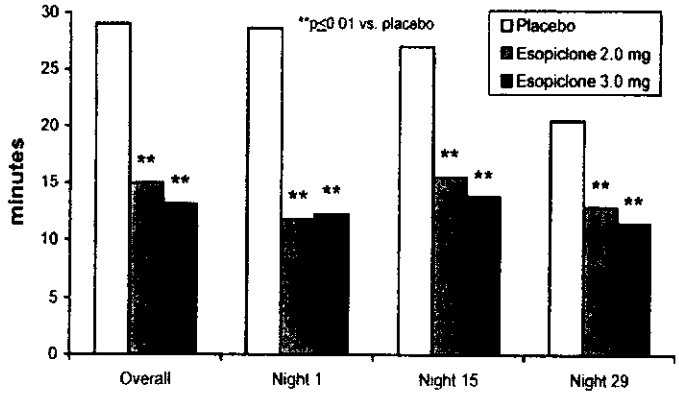
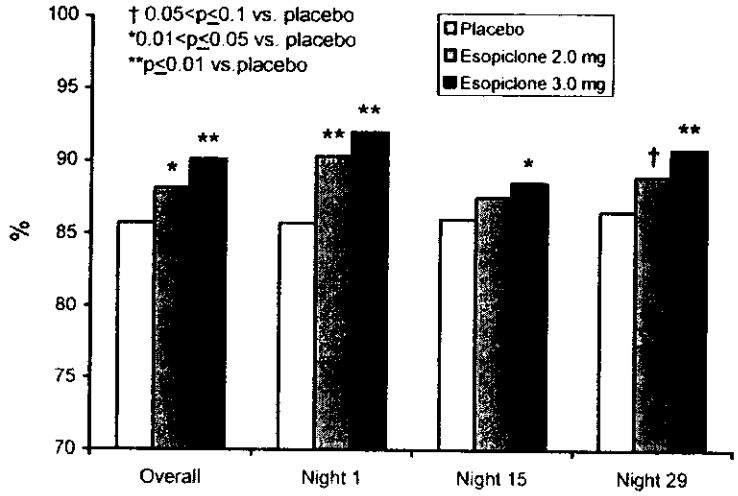
Figure VIC3. Panels A-C. Study 190-046 Efficacy Results (ITT Population).

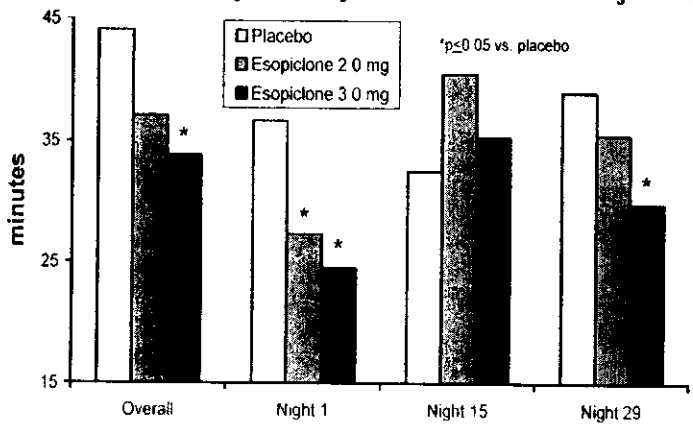
Panel A. Primary Efficacy Variable: Median Objective LPS



Panel B. "Key" Secondary Efficacy Variable: the Median Objective Sleep Efficiency



Panel B. A Secondary Efficacy Variable: Median Objective WASO



Note: "Overall" represents the average of all double-blind assessments. The pairwise comparison was performed using the appropriate contrast within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure.

Table VIC11 Panels A-B Summary Tables on Efficacy Results (ITT Population) in Study 190-046

Panel A. Primary Variable: Objective LPS

Objective Latency to Persistent Sleep (minutes)	Placebo (n=99)	Esopiclone 2.0 mg (n=104)	Esopiclone 3.0 mg (n=105)
Entire Double-Blind Period			
N	99	104	105
Mean (SD)	33.0 (22.6)	23.0 (24.9)	18.0 (15.7)
Median	29.0	15.0	13.1
Min, Max		—	
Pairwise p-value vs. placebo		<0.0001	<0.0001
Night 1			
N	96	102	105
Mean (SD)	35.2 (28.0)	21.4 (27.6)	17.5 (20.2)
Median	28.6	11.8	12.3
Min, Max		—	
Pairwise p-value vs. placebo		<0.0001	<0.0001
Night 15			
N	95	97	100
Mean (SD)	34.0 (28.0)	21.9 (21.1)	19.5 (19.6)
Median	27.0	15.5	13.8
Min, Max		—	
Pairwise p-value vs. placebo		<0.0001	<0.0001
Night 29			
N	95	98	100
Mean (SD)	30.2 (28.2)	24.0 (35.8)	18.1 (26.1)
Median	20.5	12.9	11.5
Min, Max		—	
Pairwise p-value vs. placebo		0.0009	<0.0001

Note: The pairwise comparison was performed using the appropriate contrast within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure.

Reference: Table 14.2.1

Panel B. "Key" Secondary Efficacy Variable: Objective Sleep Efficiency

Objective Sleep Efficiency (%)	Placebo (n=99)	Esopiclone 2.0 mg (n=104)	Esopiclone 3.0 mg (n=105)
Entire Double-Blind Period			
N	99	104	105
Mean (SD)	83.5 (8.9)	86.5 (7.6)	88.8 (5.7)
Median	85.7	88.1	90.1
Min, Max		—	
Pairwise p-value vs. placebo		0.0059	<0.0001
Night 1			
N	96	102	105
Mean (SD)	83.8 (9.2)	89.3 (7.0)	90.3 (6.2)
Median	85.7	90.3	92.0
Min, Max		—	
Pairwise p-value vs. placebo		<0.0001	<0.0001
Night 15			
N	95	97	100
Mean (SD)	83.4 (10.5)	85.0 (10.1)	87.4 (8.9)
Median	86.0	87.5	88.5
Min, Max		—	
Pairwise p-value vs. placebo		0.2025	0.0043
Night 29			
N	95	98	100
Mean (SD)	82.9 (11.7)	86.2 (9.6)	88.4 (8.5)
Median	86.5	88.9	90.8
Min, Max		—	
Pairwise p-value vs. placebo		0.0557	0.0001

Note: The pairwise comparison was performed using the appropriate contrast within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure.

Table VIC12 Panels A-B, Continued. Summary Tables on Efficacy Results (ITT Population) in Study 190-046

Panel A. Secondary Variable: Objective WASO

Objective WASO (minutes)	Placebo (n=99)	Esopiclone 2.0 mg (n=104)	Esopiclone 3.0 mg (n=105)
Entire Double-Blind Period			
N	99	104	105
Mean (SD)	50.0 (34.5)	44.5 (29.4)	38.0 (26.7)
Median	44.1	37.1	33.8
Min, Max			
Pairwise p-value vs. placebo		0.2564	0.0055
Night 1			
N	96	102	105
Mean (SD)	47.1 (37.3)	32.4 (24.0)	31.7 (24.7)
Median	36.6	27.3	24.5
Min, Max			
Pairwise p-value vs. placebo		0.0062	0.0015
Night 15			
N	95	97	100
Mean (SD)	49.6 (42.1)	52.9 (41.3)	43.8 (39.1)
Median	33.0	40.5	35.3
Min, Max			
Pairwise p-value vs. placebo		0.3193	0.5203
Night 29			
N	95	98	100
Mean (SD)	54.5 (47.5)	44.9 (34.7)	39.5 (34.0)
Median	39.0	35.5	29.8
Min, Max			
Pairwise p-value vs. placebo		0.3564	0.0247

Note: The pairwise comparison was performed using the appropriate contrast within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure

Reference: Table 14.2.3

Panel B. Other Secondary Objective and Subjective Sleep Variables

Efficacy Measure	Placebo (n=99)	Esopiclone 2.0 mg (n=104)	Esopiclone 3.0 mg (n=105)
Objective Measures			
Number of Awakenings	6.0	6.5	5.7
Wake Time Before Persistent Sleep (min)	22.0	12.2**	11.2**
Wake Time During Sleep (min)	35.2	30.1	27.2**
Wake Time After Sleep (min)	1.0	2.5	2.3
Subjective Measures			
Sleep Latency[1] (min)	46.0 (46.0)	30.0** (29.5**)	27.7** (25.0**)
Total Sleep Time[1] (min)	366.0 (366.0)	400.0* (399.0*)	406.0** (406.0**)
Number of Awakenings	3.0	2.7	2.4
WASO[1] (min)	45.0 (45.0)	37.1 (37.1)	30.2* (30.2*)
Quality of Sleep (mm)	47.7	54.5*	56.6**
Depth of Sleep (mm)	51.7	58.9**	56.7*
Morning Sleepiness (mm)	47.7	50.9	51.0

*0.01<p≤0.05; **p≤0.01. The pairwise comparison was performed using the appropriate contrast within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure.

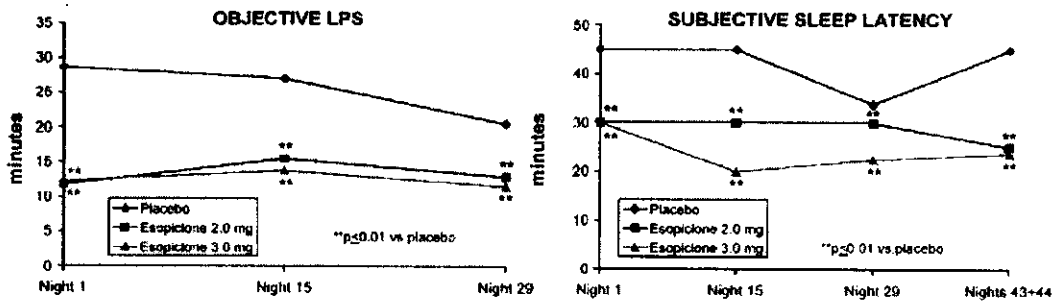
[1]Results in parentheses represent data with values >540 minutes removed (see Section 11.1).

All values represent group medians unless otherwise indicated

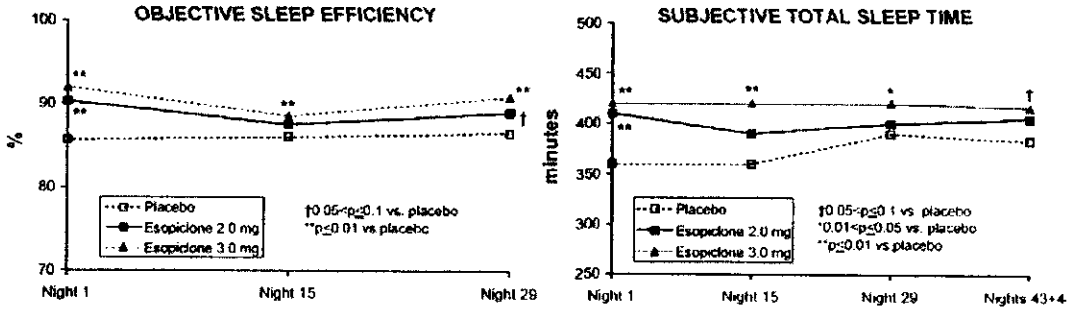
Reference: Tables 14.2.4.1, 14.2.4.2, 14.2.4.3, 14.2.4.4, 14.2.6.1, 14.2.6.1.1, 14.2.6.2, 14.2.6.2.1, 14.2.6.3, 14.2.6.4, 14.2.6.4.1, 14.2.6.5, 14.2.6.6, and 14.2.6.7

Figure VIC4 Panels A-C. Primary, "Key" Secondary and Secondary Objective and Subjective Sleep Variable Results (Median Values) Over Time of Study 190-046 (ITT Population).

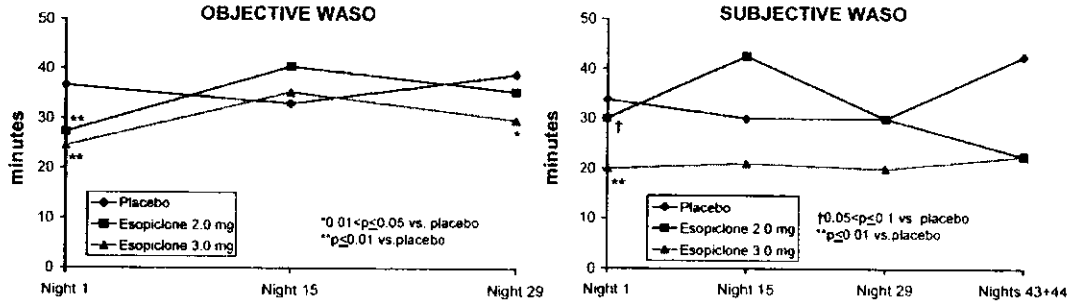
Panel A. Primary Variable (Objective LPS) and a Secondary Variable (Subjective LPS)



Panel B. "Key" Secondary Variable (Objective Sleep Efficiency) and Secondary Variable (Subjective Total Sleep Time)



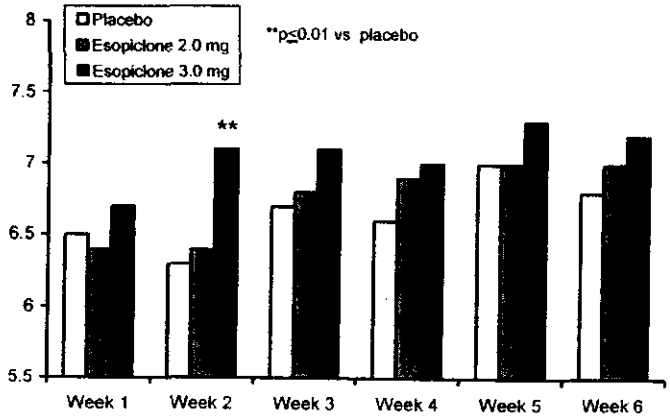
Panel C. Secondary Variables (Objective and Subjective WASO)



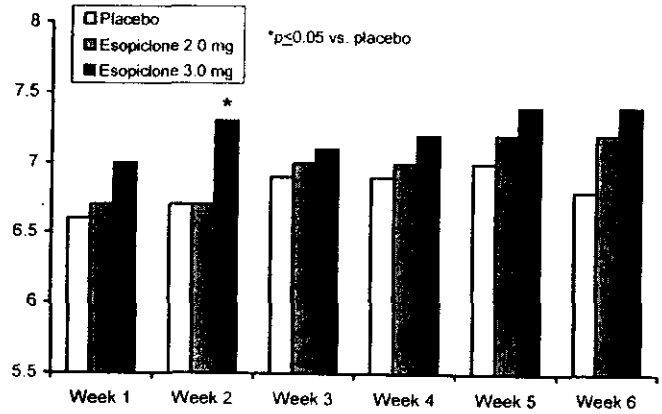
References for Figures 11.4.1.5-1 through 11.4.1.5-3: Tables 14.2.1, 14.2.2, 14.2.3, 14.2.6.1.1, 14.2.6.2.1, and 14.2.6.4.1. The pairwise comparison was performed using the appropriate contrasts within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. Subjective sleep latency, subjective WASO, and subjective total sleep time data have values >540 minutes removed (see Section 11.1). The sample sizes for subjective measures at Days 43 and 44 were small, resulting in reduced statistical power (see Section 9.8.1). All values represent group medians.

Figure VIC5 Panels A-B. Results on "Next Day Effects" Parameters (ITT Population) of Study 190-046

Panel A. Median Daytime Alertness



Panel B. Median Daytime Ability to Function



Note: Week 1 (Nights 2-8), 2 (Nights 9-15), 3 (Nights 16-22), 4 (Nights 23-29), 5 (Nights 30-36), and 6 (Nights 37-44). Measurements are based on a scale of 0 = poor and 10 = excellent from the Evening Questionnaire. The pairwise comparison was performed using the appropriate contrast within an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure.

References: Tables 14.2.8.1 and 14.2.8.2.

Table VIC13. DSST Results in Study 190-046.

Treatment	Morning	Absolute Score			Change from Baseline Score			P-value[1]
		N	Mean (SD)	Median	N	Mean (SD)	Median	
Placebo (n=99)	Baseline	98	56.7 (14.58)	57.0	--	--	--	--
	1	99	59.1 (12.83)	60.0	98	2.4 (8.5)	3.0	--
	15	96	58.6 (13.86)	59.0	96	2.5 (8.2)	3.0	--
	29	95	61.1 (14.03)	60.5	95	4.7 (9.1)	4.0	--
	45+46	95	60.4 (13.15)	61.0	95	4.2 (10.0)	4.5	--
Esopiclone 2.0 mg (n=105)	Baseline	103	57.2 (14.24)	56.0	--	--	--	--
	1	103	60.1 (14.15)	59.5	102	3.1 (10.8)	4.0	0.9442
	15	100	60.4 (12.95)	60.3	100	2.8 (9.3)	3.5	0.5095
	29	99	60.0 (14.35)	59.0	99	2.4 (9.1)	3.0	0.0912
	45+46	97	61.3 (13.38)	61.0	97	3.6 (8.9)	5.5	0.8741
Esopiclone 3.0 mg (n=104)	Baseline	102	59.2 (12.10)	60.0	--	--	--	--
	1	104	60.1 (12.39)	61.0	101	0.6 (8.7)	2.0	0.0195
	15	102	60.9 (11.85)	61.5	99	1.4 (8.0)	1.0	0.2641
	29	101	61.8 (16.11)	62.0	98	2.8 (12.4)	3.0	0.0807
	45+46	101	62.8 (12.51)	64.5	98	3.4 (8.7)	3.5	0.6919

[1]Change from baseline was compared to placebo by day using an ANOVA model on rank-transformed data with treatment and site as fixed effects.

Note: Baseline was the baseline visit (Visit 2 single-blind placebo) assessment. For each visit, if a subject had more than one assessment, the values were averaged.

Reference: Table 14.3.6.

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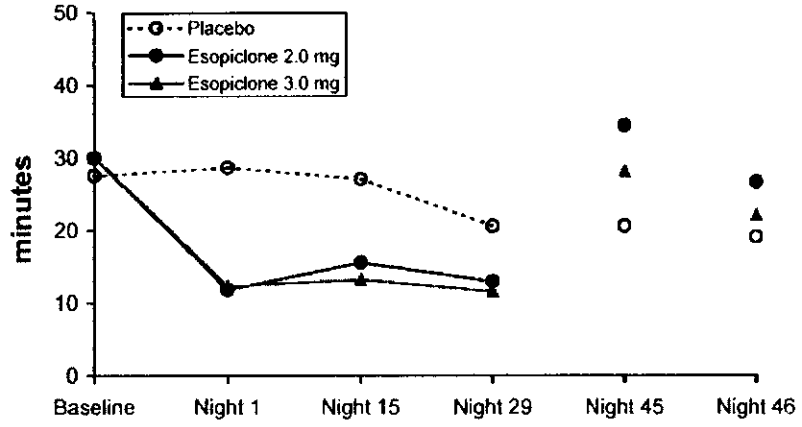
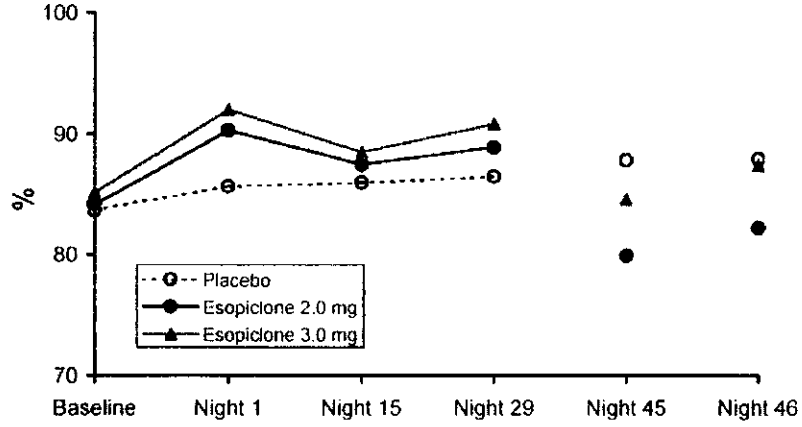
Figures VIC6. Panels A-C. Results on Discontinuation (Rebound) Effects of Study 190-046 (ITT Population)

Panel A. Median Objective LPS.



Panel B. Median Objective Sleep Efficiency



Panel C. Median Objective WASO

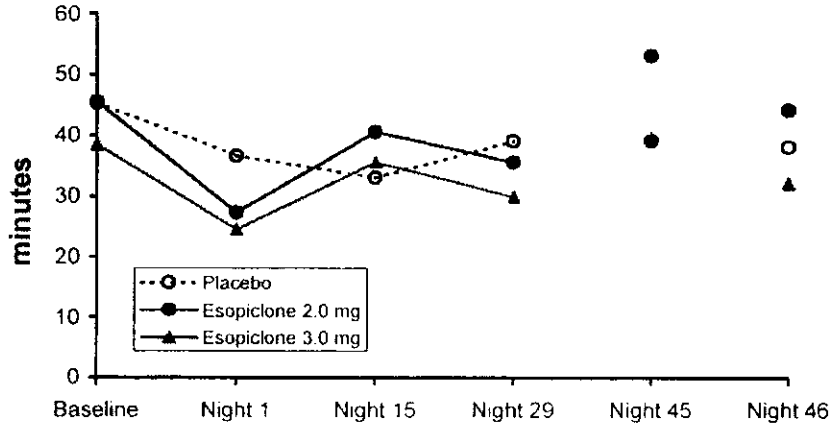


Table VIC14. Results on Discontinuation (Rebound) Effects of Study 190-046 (ITT Population) in Summary Tables

Change from Baseline on Objective LPS (minutes)			Change from Baseline (minutes)				
Treatment	Night	N	Mean (SD)	Median	Min, Max	Within treatment p-value[1]	Pairwise p-value vs. placebo[2]
Placebo (n=99)	45	93	-7.1 (48.7)	-6.0		0.0307	--
	46	91	-9.7 (40.5)	-6.0		0.0008	--
	Average	93	-8.3 (39.7)	-4.0		0.0348	--
Esopiclone 2.0 mg (n=105)	45	93	6.6 (49.3)	2.0		0.2746	0.0458
	46	92	1.0 (48.1)	-2.6		0.8287	0.0818
	Average	94	3.4 (40.3)	2.4		0.2525	0.0296
Esopiclone 3.0 mg (n=104)	45	99	10.5 (65.9)	-0.5		0.5982	0.1642
	46	98	-12.7 (44.8)	-8.5		0.0004	0.7991
	Average	99	-1.2 (46.8)	-0.3		0.3981	0.5212
Change from Baseline on Objective Sleep Efficiency (%)							
Placebo (n=99)	45	93	1.9 (15.7)	2.6	-57.9, 39.9	0.0355	--
	46	91	2.1 (14.2)	4.1	-61.5, 34.0	0.0128	--
	Average	93	2.1 (13.7)	2.9	-50.7, 36.9	0.0362	--
Esopiclone 2.0 mg (n=105)	45	93	-3.3 (15.3)	-2.5	-45.1, 65.3	0.0041	0.0008
	46	92	-1.2 (16.0)	0.9	-68.4, 51.6	0.8167	0.0746
	Average	94	-2.2 (12.8)	-2.2	-33.3, 58.4	0.0132	0.0018
Esopiclone 3.0 mg (n=104)	45	99	-3.6 (18.4)	-1.0	-64.9, 49.3	0.1402	0.0221
	46	98	3.2 (15.0)	3.7	-50.7, 54.0	0.0116	0.9019
	Average	99	-0.1 (14.8)	1.0	-57.8, 49.5	0.9461	0.2179
Change from Baseline on Objective WASO (minutes)							
Placebo (n=99)	45	93	-2.9 (57.3)	-9.0		0.1324	--
	46	91	-1.8 (56.8)	-6.5		0.0818	--
	Average	93	-2.5 (48.3)	-4.0		0.4097	--
Esopiclone 2.0 mg (n=105)	45	93	8.7 (62.2)	7.0		0.0426	0.0119
	46	92	2.4 (60.9)	-3.0		0.7880	0.3957
	Average	94	5.5 (52.7)	5.0		0.1028	0.0983
Esopiclone 3.0 mg (n=104)	45	99	8.0 (62.9)	2.5		0.2807	0.0953
	46	98	-4.0 (52.0)	-7.5		0.1142	0.9890
	Average	99	1.8 (50.8)	2.3		0.5531	0.4518

[1]For each treatment group, the change from baseline was analyzed using the Wilcoxon signed rank test.

[2]The pairwise comparison was performed using the appropriate contrasts within an ANOVA model on the rank-transformed change from baseline data with treatment and site as fixed effects. The analysis compared each esopiclone dose group to the placebo group using the MIXED procedure.

Note: "Baseline" was the Visit 2 single-blind assessment. (For subjects who had two nights of single-blind treatment, the values were

Table VIC15. Schedule of Assessments in Study 190-049 6-month Double-blind/6-month Open-Label Subjective Sleep Trial in Non-Elderly Patients with Chronic Insomnia

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	X													
[redacted]	X	X												
[redacted]	X	X												
[redacted]	X													
[redacted]	X[1]													
[redacted]	X[1]													
[redacted]	X[1]													
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X			X			X			X			X	X
[redacted]	X[2]	X[2]												
[redacted]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X													
[redacted]	X														X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]	X	X													
[redacted]		X	X	X	X	X	X	X[4]	X	X	X	X	X		
[redacted]			X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]		X			X			X			X			X	X
[redacted]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	

1- As outlined in Section 13.2 Visit 1 (Screening).
2- Per Amendment 3, this evaluation was not performed., see Section 9.8.1.
3- Weekly (q 7 days ± 1 day), at the evening. The first one is to be done in the evening of the Baseline visit, prior to first dose. The last one is done in the evening of the End-of-Study visit (Visit 15).
4- Subject completing through Visit 8 may be continued on study on open-label escitalopram 3 mg for remainder of study.

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Table VIC 16. Study 190-049: Efficacy Variables.

Primary Efficacy Variable

Sleep latency (minutes): Subjective average time to fall asleep over the past week. The last-three-month average (Month 4-6) for sleep latency during the double-blind treatment period was the primary efficacy endpoint.

Key Secondary Efficacy Variable

Total sleep time (minutes): Subjective average duration of sleep over the past week. The last-three-month average (Month 4-6) for total sleep time during the double-blind treatment period was the key secondary efficacy endpoint.

Other Secondary Efficacy Variables

The first-three-month averages and the last-three-month averages during the double-blind period, as well as the monthly averages during each treatment period (double-blind, open-label, and overall esopiclone) for the following subjective sleep variables were secondary efficacy endpoints:

- Sleep latency (except double-blind last-three-month average, which is the primary efficacy variable);
- Total sleep time (except double-blind last-three-month average, which is the key secondary efficacy variable);
- Number of awakenings: Average number of times awake during the night;
- Wake time after sleep onset (WASO) (minutes): Average time awake after first falling asleep;
- Quality of sleep: Measured on a discrete analog scale from 0 to 10 where 0 = poor and 10 = excellent;
- Number of nights awakened: Number of nights during the week that subject awoke after falling asleep (minimum = 0, maximum = 7).

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Table VIC17. Mean Daily Dose (mg/day) of Placebo and 2 mg ESZ/day Treatment Groups during the 6- month Double-Blind Phase of Study 190-049 (A subjective sleep study in non-elderly patients with Chronic Insomnia).

	Average Daily Dose (mg/day)				
	Placebo (N=195) n (%)	Esopiclone (N=593)			
Duration of Treatment		<1 mg n (%)	1-<2 mg n (%)	2-<2.75mg n (%)	≥2.75 mg n (%)
≤1 month	36 (19.4)	0 (0.0)	4 (0.7)	16 (2.8)	38 (6.7)
>1-2 months	13 (7.0)	1 (0.2)	5 (0.9)	11 (1.9)	26 (4.6)
>2-3 months	12 (6.5)	0 (0.0)	4 (0.7)	15 (2.7)	24 (4.3)
>3-4 months	9 (4.8)	0 (0.0)	3 (0.5)	8 (1.4)	18 (3.2)
>4-5 months	4 (2.2)	0 (0.0)	1 (0.2)	3 (0.5)	10 (1.8)
>5-6 months	49 (26.3)	0 (0.0)	13 (2.3)	28 (5.0)	136 (24.2)
>6 months	63 (33.9)	0 (0.0)	11 (2.0)	44 (7.8)	144 (25.6)
Total Subjects	186 (100.0)	1 (0.2)	41 (7.3)	125 (22.2)	396 (70.3)

Note: This table summarizes data for Population A + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: Average daily dose was calculated as the total amount of drug taken divided by the number of days between the first dispensation and (the minimum of the end of the double-blind treatment period or the last dose date on the study termination page).

Note: Percentages are based on subjects in each treatment group who had non-missing values for average daily dose.

Reference: Table 14.1.6A.

Table VIC18. Mean Daily Dose (mg/day) for the 6- month Open-Label Phase (2 mg ESZ/Day)of Study 190-049

	Average Daily Dose[1] (mg/day) by Previous Double-blind Treatment							
	Placebo (N=111)				Esopiclone (N=360)			
Duration of Open-label Treatment	<1 mg n (%)	1-<2 mg n (%)	2-<2.75 mg n (%)	≥2.75 mg n (%)	<1 mg n (%)	1-<2 mg n (%)	2-<2.75 mg n (%)	≥2.75 mg n (%)
≤1 month	0 (0.0)	0 (0.0)	2 (1.8)	4 (3.7)	1 (0.3)	0 (0.0)	3 (0.8)	11 (3.1)
>1-2 months	0 (0.0)	1 (0.9)	0 (0.0)	4 (3.7)	0 (0.0)	1 (0.3)	1 (0.3)	11 (3.1)
>2-3 months	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.6)	0 (0.0)	1 (0.3)	1 (0.3)	4 (1.1)
>3-4 months	0 (0.0)	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.7)
>4-5 months	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	1 (0.3)	0 (0.0)	10 (2.8)
>5-6 months	0 (0.0)	4 (3.7)	6 (5.5)	33 (30.3)	0 (0.0)	9 (2.5)	25 (7.0)	128 (35.9)
>6 months	0 (0.0)	0 (0.0)	6 (5.5)	38 (34.9)	0 (0.0)	6 (1.7)	23 (6.5)	114 (32.0)
Total Subjects	0 (0.0)	7 (6.4)	17 (15.6)	85 (78.0)	1 (0.3)	18 (5.1)	53 (14.9)	284 (79.8)

[1] All subjects received esopiclone 3 mg during the open-label treatment period.

Note: This table summarizes data for Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: Average daily dose was calculated as the total amount of drug taken divided by the number of days between the first dispensation and the minimum of (the end of the open-label treatment period or the last dose date on the study termination page).

Note: Percentages are based on subjects in each treatment group who had non-missing values for average daily dose.

Reference: Table 14.1.4B.

Table VIC19. Mean Daily Dose (mg/day) for the First 6 Months of ESZ Treatment (of either Double-blind or Open Label ESZ) in Study 190-049

	Average Daily Dose (mg/day)			
	Esopiclone[1] (N=704)			
Duration of Treatment	<1 mg n (%)	1-<2 mg n (%)	2-<2.75 mg n (%)	≥2.75 mg n (%)
≤1 month	0 (0.0)	4 (0.6)	18 (2.7)	42 (6.2)
>1-2 months	1 (0.1)	6 (0.9)	11 (1.6)	30 (4.5)
>2-3 months	0 (0.0)	4 (0.6)	15 (2.2)	29 (4.3)
>3-4 months	0 (0.0)	5 (0.7)	10 (1.5)	18 (2.7)
>4-5 months	0 (0.0)	1 (0.1)	4 (0.6)	11 (1.6)
>5-6 months	0 (0.0)	17 (2.5)	34 (5.1)	169 (25.1)
>6 months	0 (0.0)	11 (1.6)	50 (7.4)	182 (27.1)
Total Subjects	1 (0.1)	48 (7.1)	142 (21.1)	481 (71.6)

[1] 6-month esopiclone 3 mg: includes the first 6 months on esopiclone 3 mg for subjects who received at least one dose of esopiclone.

Note: This table summarizes data for Population B + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: Average daily dose was calculated as the total amount of drug taken divided by the number of days between the first dispensation and the minimum of the end of the treatment period or the last dose date on the study termination page.

Note: Percentages are based on subjects in the treatment group who had non-missing values for average daily dose.

Reference: Table 14.1.4C.

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Table VIC20. Mean Daily Dose (mg/day) for 12 Months of ESZ Treatment (Double-blind and Open Label ESZ) in Study 190-049

	Average Daily Dose (mg/day)			
	Esopiclone[1] (N=593)			
Duration of Treatment	<1 mg n (%)	1-<2 mg n (%)	2-<2.75 mg n (%)	≥2.75 mg n (%)
≤1 month	0 (0.0)	4 (0.7)	16 (2.8)	38 (6.7)
>1-2 months	1 (0.2)	5 (0.9)	11 (2.0)	26 (4.6)
>2-3 months	0 (0.0)	4 (0.7)	15 (2.7)	24 (4.3)
>3-4 months	0 (0.0)	3 (0.5)	8 (1.4)	18 (3.2)
>4-5 months	0 (0.0)	1 (0.2)	3 (0.5)	10 (1.8)
>5-6 months	0 (0.0)	3 (0.5)	2 (0.4)	10 (1.8)
>6-7 months	0 (0.0)	0 (0.0)	3 (0.5)	17 (3.0)
>7-8 month	0 (0.0)	1 (0.2)	0 (0.0)	12 (2.1)
>8-9 months	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.5)
>9-10 months	0 (0.0)	0 (0.0)	1 (0.2)	5 (0.9)
>10-11 months	0 (0.0)	1 (0.2)	0 (0.0)	10 (1.8)
>11-12 months	0 (0.0)	10 (1.8)	30 (5.3)	122 (21.7)
>12 months	0 (0.0)	4 (0.7)	26 (4.6)	113 (20.1)
Total Subjects	1 (0.2)	36 (6.4)	118 (21.0)	408 (72.5)

[1] 12-month esopiclone 3 mg: includes up to 12 months on esopiclone 3 mg for subjects who were randomized to esopiclone 3 mg and received at least one dose of esopiclone in the double-blind or open-label periods.

Note: This table summarizes data for Population C + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: Average daily dose was calculated as the total amount of drug taken divided by the number of days between the first dispensation and the minimum of the end of the treatment period or the last dose date on the study termination page.

Note: Percentages are based on subjects in the treatment group who had non-missing values for average daily dose.

Reference: Table 14.1.4C.

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Table VIC21. Efficacy Results on Subjective Sleep Latency from the 6- month Double-Blind Phase of Study 190-049 (A subjective sleep study in non-elderly patients with Chronic Insomnia).
ITT Population

Time Interval	Statistic	Placebo (n=195)	Esopiclone 3 mg (n=593)	P-value
Month 4-6 Average [primary endpoint]	Mean (SD)	64.7 (56.4)	46.7 (45.6)	<0.0001
	Median	44.8	31.7	
	Min, Max	4.1, 330.0	2.1, 565.0	
Month 1-3 Average	Mean (SD)	66.1 (54.8)	45.3 (40.0)	<0.0001
	Median	50.8	32.1	
	Min, Max	5.0, 330.0	4.8, 373.3	
Month 1	Mean (SD)	71.3 (59.8)	44.3 (36.5)	<0.0001
	Median	52.5	31.3	
	Min, Max			
Month 2	Mean (SD)	65.4 (56.9)	45.1 (46.2)	<0.0001
	Median	50.0	30.0	
	Min, Max			
Month 3	Mean (SD)	63.2 (57.1)	46.3 (53.9)	<0.0001
	Median	45.0	30.0	
	Min, Max			
Month 4	Mean (SD)	64.3 (59.8)	47.8 (49.8)	<0.0001
	Median	45.0	30.0	
	Min, Max			
Month 5	Mean (SD)	66.6 (74.6)	45.3 (45.4)	<0.0001
	Median	43.8	30.0	
	Min, Max			
Month 6	Mean (SD)	63.1 (57.9)	47.0 (50.6)	<0.0001
	Median	45.0	30.0	
	Min, Max			

Note: This table summarizes data for Population A 1 C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: For each subject, "Month 1-3 Average" represents the average over Months 1-3 of the double-blind period, and "Month 4-6 Average" represents the average over Months 4-6 of the double-blind period based on the last observation carried forward algorithm. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used.

Note: The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference: Tables 14.2.1.1.1A

Table VIC22. Results of the "Key" Secondary Efficacy Variable, Subjective Total Sleep Time in the Double-blind Phase of Study 190-049 (ITT Population).

Time Interval	Statistic	Placebo (n=195)	Esopiclone 3 mg (n=593)	P-value
Month 4-6 Average [key secondary endpoint]	Mean (SD)	341.1 (72.4)	377.3 (69.2)	<0.0001
	Median	345.1	381.7	
	Min, Max	136.0, 500.0	73.2, 555.0	
Month 1-3 Average	Mean (SD)	338.1 (67.2)	377.1 (63.7)	<0.0001
	Median	342.5	382.5	
	Min, Max	137.5, 486.7	79.6, 555.0	
Month 1	Mean (SD)	333.1 (69.8)	373.9 (67.5)	<0.0001
	Median	337.5	375.0	
	Min, Max			
Month 2	Mean (SD)	339.1 (79.8)	379.7 (68.9)	<0.0001
	Median	345.0	385.0	
	Min, Max			
Month 3	Mean (SD)	341.7 (69.6)	378.2 (70.5)	<0.0001
	Median	348.8	382.5	
	Min, Max			
Month 4	Mean (SD)	345.6 (73.6)	375.6 (72.1)	<0.0001
	Median	360.0	379.4	
	Min, Max			
Month 5	Mean (SD)	338.4 (77.9)	377.8 (71.7)	<0.0001
	Median	340.6	382.5	
	Min, Max			
Month 6	Mean (SD)	339.3 (77.1)	378.3 (72.3)	<0.0001
	Median	345.0	382.5	
	Min, Max			

Note: This table summarizes data for Population A + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: For each subject, "Month 1-3 Average" represents the average over Months 1-3 of the double-blind period, and "Month 4-6 Average" represents the average over Months 4-6 of the double-blind period based on the last observation carried forward algorithm. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used.

Note: The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference: Tables 14.2.1.2.1A, 14.2.1.2.2A.

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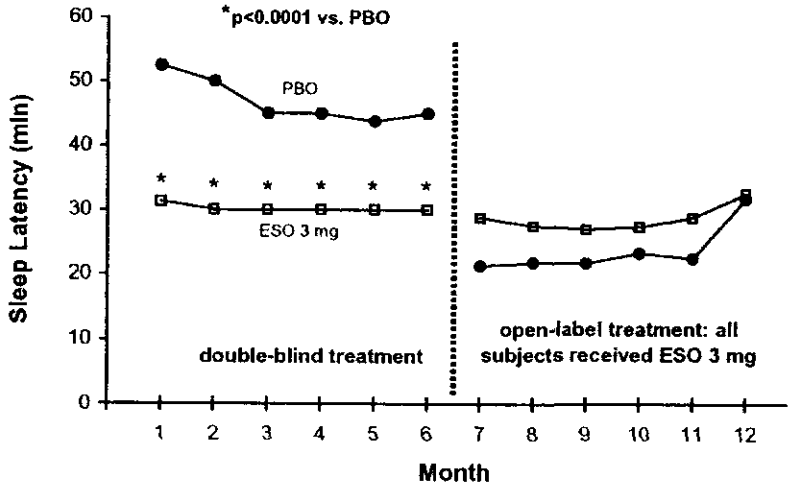
Figure VIC7. Efficacy Results on Median Subjective Sleep Latency for the Double-blind and Open Label Phases of Study 190-049 (ITT Population).

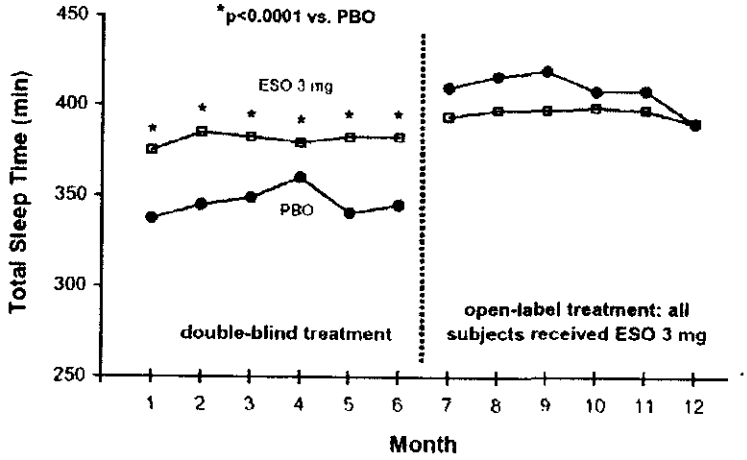


Note: This figure summarizes data for Population A + C and Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: All results are group medians. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference: Tables 14.2.1.1.2A and 14.2.1.1B.

Figure VIC8. Results of the "Key" Secondary Efficacy Variable, Median Subjective Total Sleep Time in the Double-blind and Open-label phases of Study 190-049 (ITT Population).



Note: This figure summarizes data for Population A + C and Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: All results are group medians. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference. Table 14.2.1.2.2A and 14.2.1.2B.

Table VIC23. Results of a Secondary Efficacy Variable, Subjective WASO in the Double-blind Phase of Study 190-049 (ITT Population).

Time Interval	Statistic	Placebo (n=195)	Esopiclone 3 mg (n=593)	P-value
Month 4-6 Average	Mean (SD)	52.5 (63.0)	43.0 (58.6)	0.0008
	Median	35.7	22.5	
	Min, Max	0.0, 472.5	0.0, 553.3	
Month 1-3 Average	Mean (SD)	59.2 (63.4)	44.7 (54.5)	<0.0001
	Median	39.4	26.9	
	Min, Max	0.0, 472.5	0.0, 569.2	
Month 1	Mean (SD)	62.8 (77.2)	47.4 (77.7)	<0.0001
	Median	36.7	23.8	
	Min, Max			
Month 2	Mean (SD)	58.8 (71.8)	44.4 (64.5)	0.0001
	Median	35.0	22.5	
	Min, Max			
Month 3	Mean (SD)	56.1 (67.2)	42.2 (70.1)	<0.0001
	Median	36.4	20.0	
	Min, Max			
Month 4	Mean (SD)	51.1 (63.3)	42.3 (56.9)	0.0020
	Median	31.3	21.5	
	Min, Max			
Month 5	Mean (SD)	58.5 (85.2)	42.5 (65.1)	<0.0001
	Median	34.4	21.3	
	Min, Max			
Month 6	Mean (SD)	48.2 (59.4)	44.2 (74.2)	0.0032
	Median	30.0	21.0	
	Min, Max			

Note: This table summarizes data for Population A + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: For each subject, "Month 1-3 Average" represents the average over Months 1-3 of the double-blind period, and "Month 4-6 Average" represents the average over Months 4-6 of the double-blind period based on the last observation carried forward algorithm. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used.

Note: The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure

Reference: Tables 14.2.1.4.1A, 14.2.1.4.2A.

Table VIC24. Results of a Secondary Efficacy Variable, Subjective Number of Awakenings in the Double-blind Phase of Study 190-049 (ITT Population).

Time Interval	Statistic	Placebo (n=195)	Esopiclone 3 mg (n=593)	P-value
Month 4-6 Average	Mean (SD)	2.5 (2.7)	1.9 (1.5)	<0.0001
	Median	2.2	1.6	
	Min, Max	0.0, 24.5	0.0, 9.5	
Month 1-3 Average	Mean (SD)	2.7 (2.6)	2.0 (1.3)	<0.0001
	Median	2.3	1.8	
	Min, Max	0.0, 24.5	0.0, 9.5	
Month 1	Mean (SD)	2.8 (2.6)	2.1 (1.4)	<0.0001
	Median	2.5	2.0	
	Min, Max			
Month 2	Mean (SD)	2.8 (2.8)	2.0 (1.5)	<0.0001
	Median	2.3	1.9	
	Min, Max			
Month 3	Mean (SD)	2.6 (2.7)	1.9 (1.5)	<0.0001
	Median	2.0	1.7	
	Min, Max			
Month 4	Mean (SD)	2.6 (2.6)	1.9 (1.5)	<0.0001
	Median	2.2	1.6	
	Min, Max			
Month 5	Mean (SD)	2.5 (2.7)	1.9 (1.6)	<0.0001
	Median	2.0	1.5	
	Min, Max			
Month 6	Mean (SD)	2.6 (2.7)	1.9 (1.5)	<0.0001
	Median	2.0	1.6	
	Min, Max			

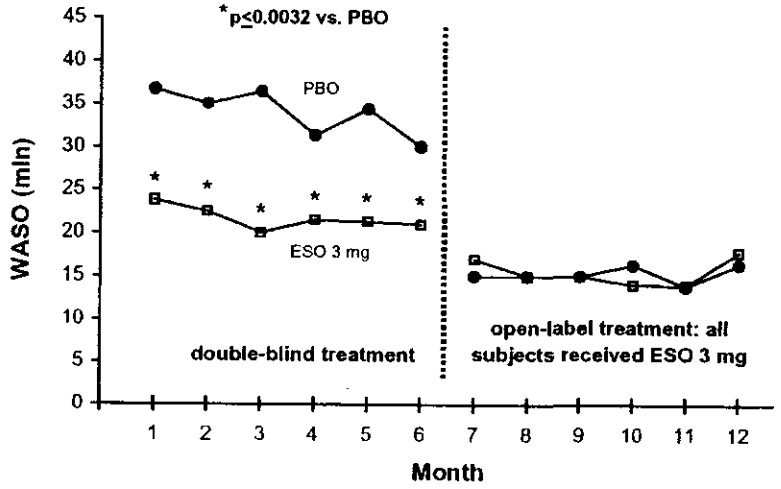
Note: This table summarizes data for Population A + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: For each subject, "Month 1-3 Average" represents the average over Months 1-3 of the double-blind period, and "Month 4-6 Average" represents the average over Months 4-6 of the double-blind period based on the last observation carried forward algorithm. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used.

Note: The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference: Tables 14.2.1.3.1A, 14.2.1.3.2A.

Figure VIC9. Results of a Secondary Efficacy Variable, Median Subjective WASO in the Double-blind and Open-Label Phases of Study 190-049 (ITT Population).

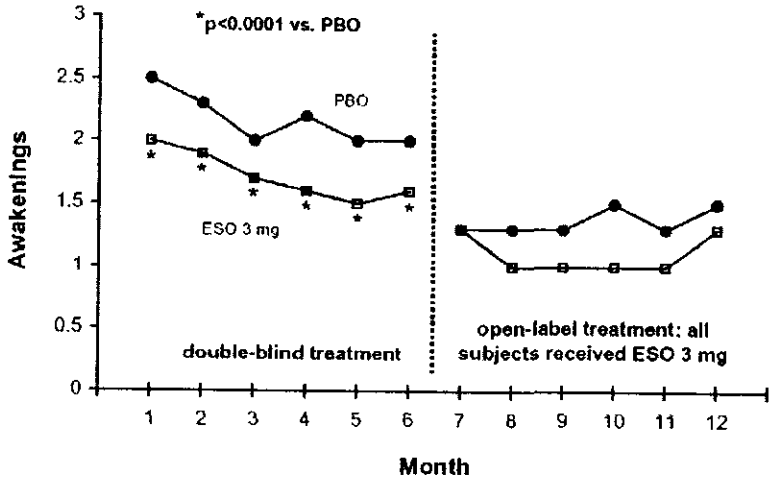


Note: This figure summarizes data for Population A + C and Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: All results are group medians. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference: Table 14.2.1.4.2A and 14.2.1.4B

Figure VIC10. Results of a Secondary Efficacy Variable, Median Subjective Number of Awakenings in the Double-blind and Open-Label Phases of Study 190-049 (ITT Population).

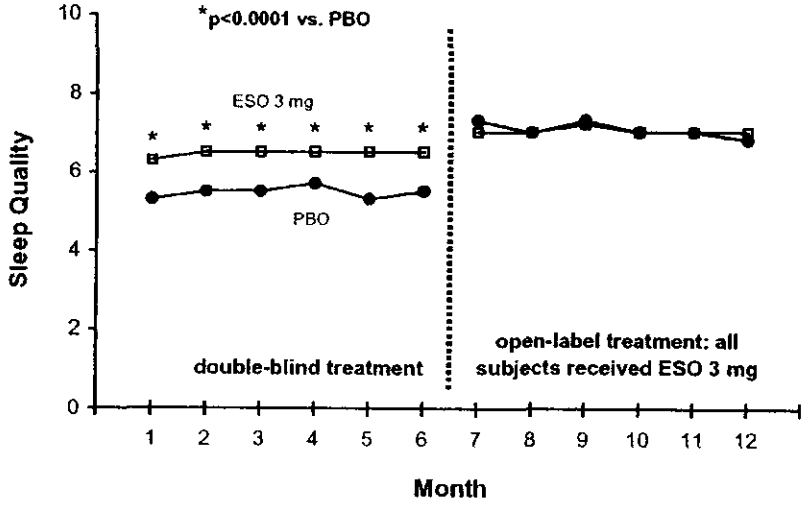


Note: This figure summarizes data for Population A + C and Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: All results are group medians. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference: Table 14.2.1.3.2A and 14.2.1.3B

Figure VIC11. Results of a Secondary Efficacy Variable, Median Subjective Quality of Sleep in the Double-blind and Open-Label Phases of Study 190-049 (ITT Population).

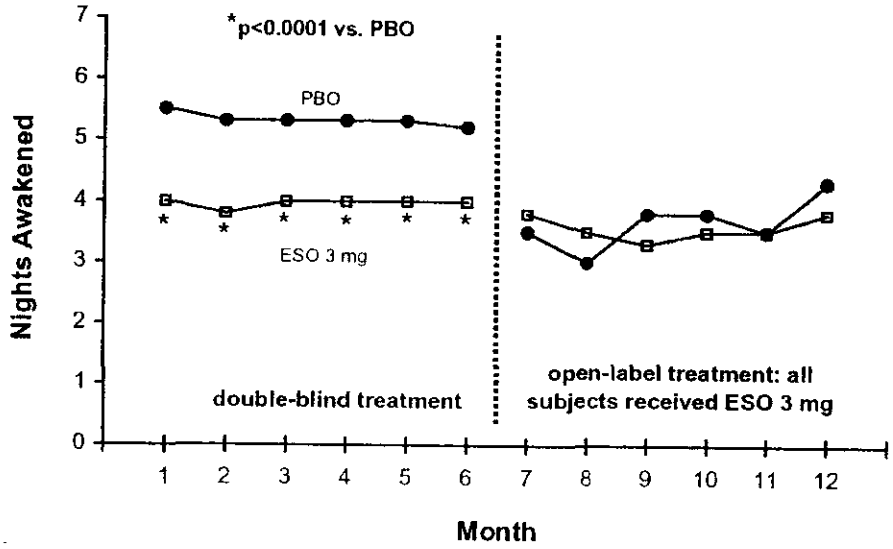


Note: This figure summarizes data for Population A + C and Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: Measured on a scale from 0=poor to 10=excellent. All results are group medians. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Reference. Table 14.2.1.5.2A and 14.2.1.5B.

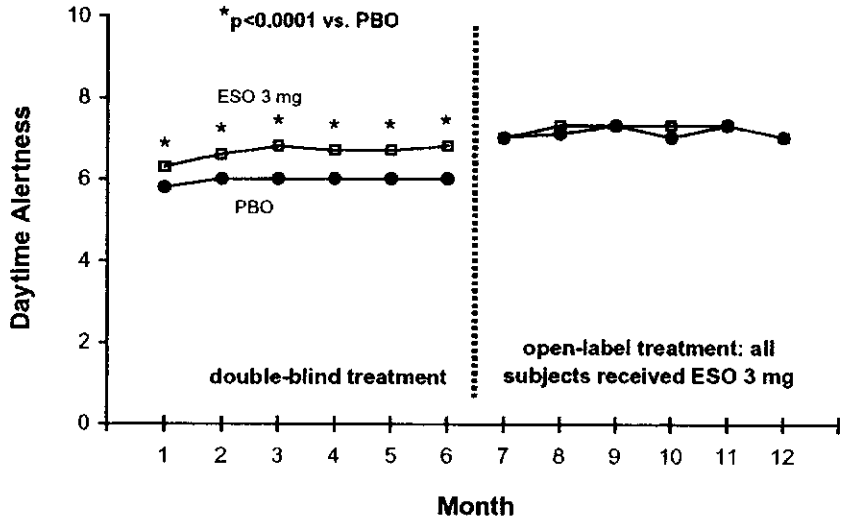
Figure VIC12. Results of a Secondary Efficacy Variable, Median Subjective Number of Awakenings in the Double-blind and Open-Label Phases of Study 190-049 (ITT Population).



Note: All results are group medians. For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

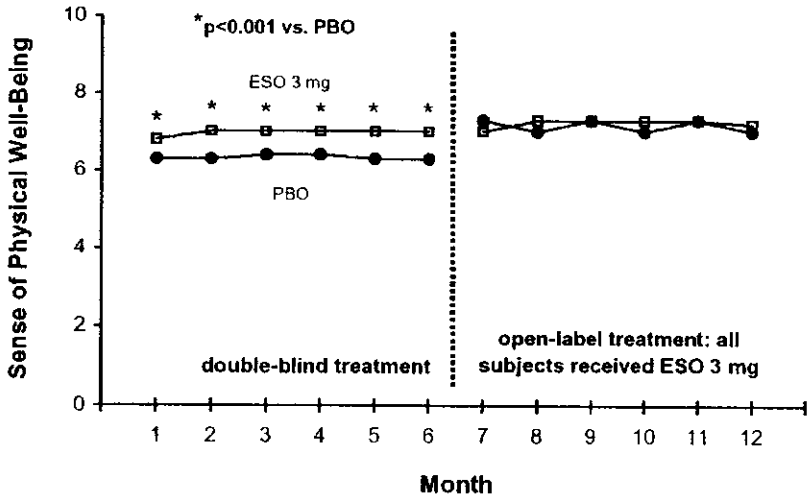
Figure VIC13. Panels A-C. Results on "Next-Day Effects" Parameters in the Double-blind and Open-Label Phases of Study 190-049 (ITT Population).

Panel A. Median Subjective Daytime Alertness*



Median values on a discrete scale from 0-10, where 0=very sleepy and 10=wake and alert.

Panel B. Median Subjective Physical Well-Being*

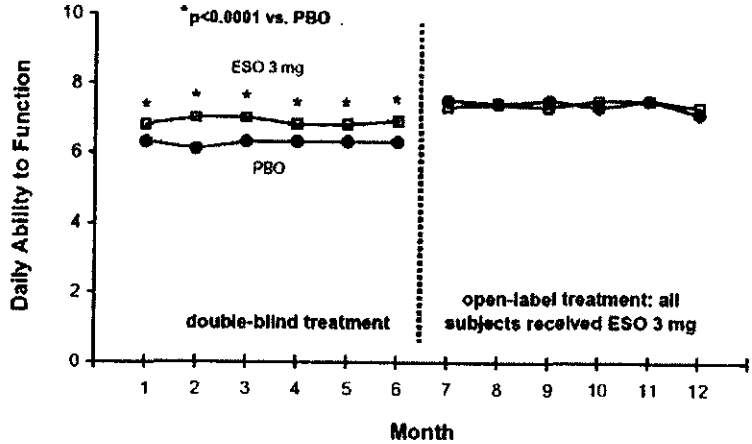


Median values on a discrete scale from 0-10 where 0=poor and 10=excellent.

* For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

Figure VIC13, continued (Panels A-C continued). Results on "Next-Day Effects" Parameters in the Double-blind and Open-Label Phases of Study 190-049 (ITT Population).

Panel C. Median Subjective Daytime Ability to Function*



Note: Median values measures on a discrete scale from 0-10 where0=poor and 10=excellent.

* For each subject, each month represents the average of all weekly data collected during that month. In the event that no data were available for a month, the previous month average was imputed. In addition, if only one value was available for a month, then the mean of that value and the previous month average was used. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared esopiclone 3 mg group to the placebo group using the MIXED procedure.

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Table VID1. Schedule of Assessments in Study 190-047 (2-Week PSG Elderly Chronic Insomnia Trial)

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Prescreening questionnaire	X							
Sleep log for median bedtime	X							
Informed Consent		X						
Inclusion/Exclusion Criteria		X						
Medical/Psychiatric History		X						
Sleep History		X						
Concomitant Medications		X	X	X		X	X	X
Physical Examination (including seated vital signs, weight, brief neurologic exam. Romberg test, heel to toe gait test)		X						X
Vital signs		X[7]	X[7]	X[7]		X[7]	X[7]	
Romberg test and heel to toe gait test		X[7]	X[7]	X[7]		X[7]	X[7]	
12-Lead Electrocardiogram (ECG)		X						
Clinical Laboratory Tests		X						X
Hepatitis B & C Test		X						
Urine Drug Screen		X[4]	X			X		
Urinalysis		X						X
Single blind placebo		X[2]						
Randomize subject/ Dispense Study Medication			X					
Double-blind study drug			X	X	X	X	X	
PSG		X[5]	X	X		X	X	
IVRS		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Quality of Life questionnaires - SF36 and ISI		X					X[8]	X[8]
Adverse Events		X	X	X		X	X	X
Medical Events Calendar (MEC)		X	X	X	X	X	X	X
Review Study Restrictions			X	X		X	X	

1. To allow for flexibility in scheduling Visit 3, Dosing Days 13 and 14 may have occurred on Days 14 and 15. Dosing was to be a minimum of 14 days. 2. Obtained each morning after PSG night. 3. Each morning prior to discharge from sleep lab (approx. 19 to 19.5 hours post lights-out). 4. Urine drug screen during screening for eligibility and at first screening PSG night. 5. Two consecutive nights after eligibility was confirmed for all other inclusion/exclusion criteria. 6. IVRS was to be called each morning and evening from Visit 1 (screening PSG) through Visit 4. 7. Prior to discharge – last morning of visit only. 8. ISI questionnaire only.

Table VID2. Schedule of Assessments in Study 190-048 (2-Week Subjective Sleep Chronic Insomnia Elderly Trial).

Observation and Procedure	Screening Visit 1 -14 to 0 Days	Baseline Visit 2	Dosing Visit 3 Week 1 (Day 8±1 day)	End-of-Study Visit 4 Week 2 (Day 15 to 17)
Informed Consent	X			
Randomization		X		
Inclusion/Exclusion Criteria	X	X		
Medical/Psychiatric History	X	X		
Sleep History	X			
Concomitant Medications	X	X	X	X
Physical Examination (including seated vital signs, weight, and brief neurologic examination)	X	X	X	X
12-Lead ECG	X		X	X
Clinical Laboratory Tests[1]	X		X	X
Hepatitis B & C Test	X			
Urine Drug Screen	X	X		
Urinalysis	X			X
Dispense Study Medication		X[2]	X	
Drug Administration Record			X	X
IVRS		X[3]	X[3]	X[3]
Quality of Life Questionnaire (Q-LES-Q)		X	X	X
Adverse Events	X	X	X	X
Medical Events Calendar (MEC)	X	X	X	X
Review Study Restrictions		X	X	

[1]Included thyroid function tests and measurement of 17β-estradiol levels.
[2]Dosing began at home on the evening of baseline visit.
[3]First IVRS call occurred at the baseline visit and again that evening prior to dosing. IVRS was called each morning and evening from Visit 2 (baseline) through Visit 4.

Table VID3. Efficacy Variables in Study 190-048

9.5.1.2.2 Key Secondary Efficacy Variable

- Subjective total sleep time (minutes): Subjective total duration of sleep assessed via IVRS.

9.5.1.2.3 Other Secondary Efficacy Variables

The following parameters were assessed each morning via IVRS.

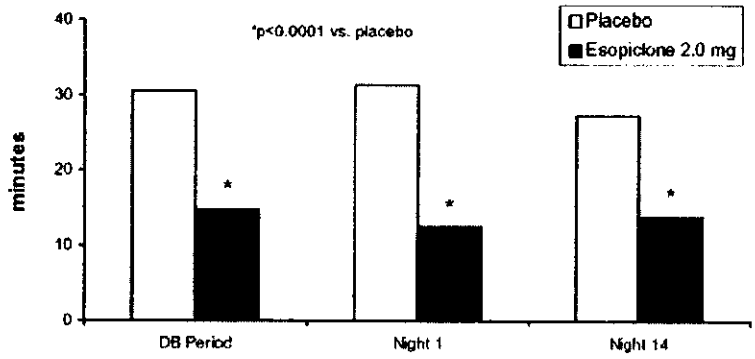
- Subjective wake time after sleep onset (WASO; minutes): Time awake after first falling asleep.
- Subjective number of awakenings: Number of times awake during sleep.
- Subjective morning sleepiness: Measured on a discrete scale from 0 to 10 where = "very sleepy" and 10 = "not at all sleepy".
- Subjective quality of Sleep: Measured on a discrete scale from 0 to 10 where 0 = "poor" and 10 = "excellent".
- Subjective depth of Sleep: Measured on a discrete scale from 0 to 10 where 0 = "very light" and 10 = "very deep".

The following parameters were assessed each evening via IVRS.

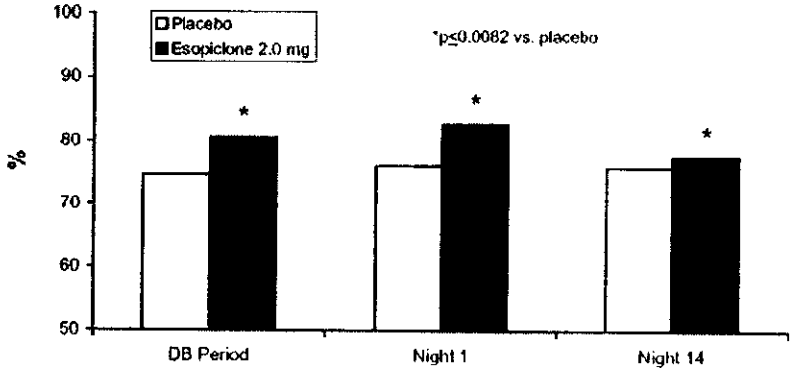
- Subjective daytime alertness: Measured on a discrete scale from 0 to 10 where 0 "drowsy" and 10 = "alert".
- Subjective number of naps taken: Number of naps taken during a given day.
- Subjective nap time (minutes): Total duration of nap time for a given day.
- Subjective daily ability to function: Measured on a discrete scale from 0 to 10 where 0 = "poor" and 10 = "excellent".
- Subjective sense of physical well-being: Measured on a discrete scale from 0 to 10 where 0 = "poor" and 10 = "excellent".

Figure VID1. Panels A-C. Efficacy Results in Study 190-047, 2-Week, PSG Study on Elderly Patients with Chronic Insomnia (ITT Population)

Panel A. Co-Primary Variable: Group Median Objective LPS



Panel B. Co-Primary Variable: Group Median Objective Sleep Efficiency



Panel C. "Key" Secondary Variable: Group Median Objective WASO

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Tables VID4. Panels A-C. Summary Tables of Efficacy Results in Study 190-047, A 2-Week PSG Study on Elderly Patients with Chronic Insomnia (ITT Population)

A. Co-Primary Variable: Group Median Objective LPS

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B. Co-Primary Variable: Group Median Objective Sleep Efficiency

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C. "Key" Secondary Variable: Group Median Objective WASO

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Table VID5. Results on Secondary Variables in Study 190-047 A 2-Week, PSG Trial on Elderly Patients with Chronic Insomnia

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Figure VID2. Results of a Secondary Analysis on a Secondary Variable: Median Objective Cumulative Wake Time at Double-Blind Dosing Night 1 in Study 190-047, A 2-Week, PSG Trial on Elderly Patients with Chronic Insomnia

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Table VI.D.5.I. Sleep Architecture Results of Study 190-047: a 2-Week, PSG Trial on Elderly Patients with Chronic Insomnia

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Figure VID3. Panels A-C. Efficacy Results in Study 190-048, A 2-Week, IVRS Subjective Sleep Study on Elderly Patients with Chronic Insomnia (ITT Population)

Panel A. Primary Variable: Median Subjective LPS

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Panel B. "Key" Secondary Variable: Median Subjective Total Sleep Time

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Panel C. Secondary Variable: Median Subjective WASO

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Table VID6. Panel A-D (see next page for Panels C and D). Summary Tables of Efficacy Results in Study 190-048, A 2-Week, IVRS Subjective Sleep Study on Elderly Patients with Chronic Insomnia (ITT Population)

Panel A. Primary Variable: Median Subjective LPS

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Panel B. "Key" Secondary Variable: Median Subjective Total Sleep Time

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Table VID6 (Panels A-D), continued. Summary Tables of Efficacy Results in Study 190-048, A 2-Week, IVRS Subjective Sleep Study on Elderly Patients with Chronic Insomnia (ITT Population)

C. Secondary Variable: Median Subjective WASO

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C. Secondary Variable: Median Subjective WASO

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Table VID7 Panels A and B. Results on "Next Day Effect" Subjective Parameters in Two 2-Week, Elderly Chronic Insomnia Trials 190-047 and 190-048 (PSG and a Subjective Sleep Studies, respectively).

Panel A. Results of PSG Trial 190-047 (Group Median Values).

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Table VID7 Panels A and B, Continued. Results on "Next Day Effect" Parameters in Elderly Chronic Insomnia Trials 190-047 and 190-048.

Panel B. Results of Subjective IVRS Sleep Trial 190-048.

Measure	Assessment	Placebo	Esopiclone 2.0 mg
Morning Sleepiness [1]	Entire DB Period	6.7	7.2†
	Week 1	6.7	7.3*
	Week 2	6.7	7.0
Daytime Alertness [2]	Entire DB Period	7.3	7.3
	Week 1	7.1	7.4
	Week 2	7.2	7.2
Number of Naps Taken (for days when a nap was observed)	Entire DB Period	3.0	2.0*
	Week 1	3.0	1.0*
	Week 2	2.0	2.0
Total Nap Time (minutes)	Entire DB Period	0.0	0.2
	Week 1	0.0	0.0
	Week 2	0.0	0.0
Daily Ability to Function [3]	Entire DB Period	7.5	7.5
	Week 1	7.4	7.6
	Week 2	7.5	7.5
Sense of Well Being [3]	Entire DB Period	7.5	7.4
	Week 1	7.3	7.6
	Week 2	7.6	7.5

†$0.05<p\leq0.1$; *$p\leq0.05$ vs. placebo. The treatment comparison was performed using an ANOVA model on the rank-transformed data with treatment and site as fixed effects. The analysis compared the esopiclone 2.0 mg group to the placebo group using the MIXED procedure.

[1] Based on a scale from 0=very sleepy to 10=not at all sleepy.

[2] Based on a scale from 0=drowsy to 10=alert.

[3] Based on a scale from 0=poor to 10=excellent.

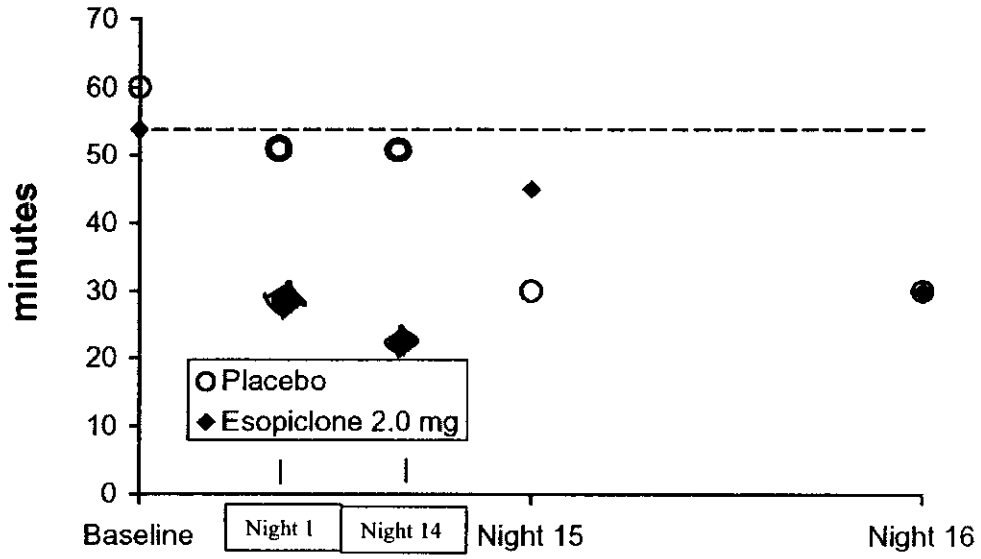
Note: "Entire double-blind period" is the average of all double-blind results; "Week 1" represents the average of Day 1 through Day 7 results; "Week 2" represents the average of remaining assessments from Day 8 to the end of the double-blind period.

Note: Values represent group medians. For each assessment, the number of subjects ranged from 40 to 128 subjects for the placebo group, and 45 to 136 for the esopiclone 2.0 mg group.

References: Tables 14.2.8.1 through 14.2.8.6.

Figure VID4 Panels A -C. Results on Subjective Sleep Parameters at Baseline, During Double-Blind Treatment (Nights 1 and 14)* and Upon Treatment Cessation (Nights 15 and 16; the 1st and 2nd Nights after Cessation) in the 2-Week Elderly Chronic Insomnia PSG Trial 190-047.

Panel A. Median Subjective Latency



***Double-blind treatment Nights 1 and 14 were added to the sponsor's version of figures A-C**

Panel B. Median Subjective Total Sleep Time

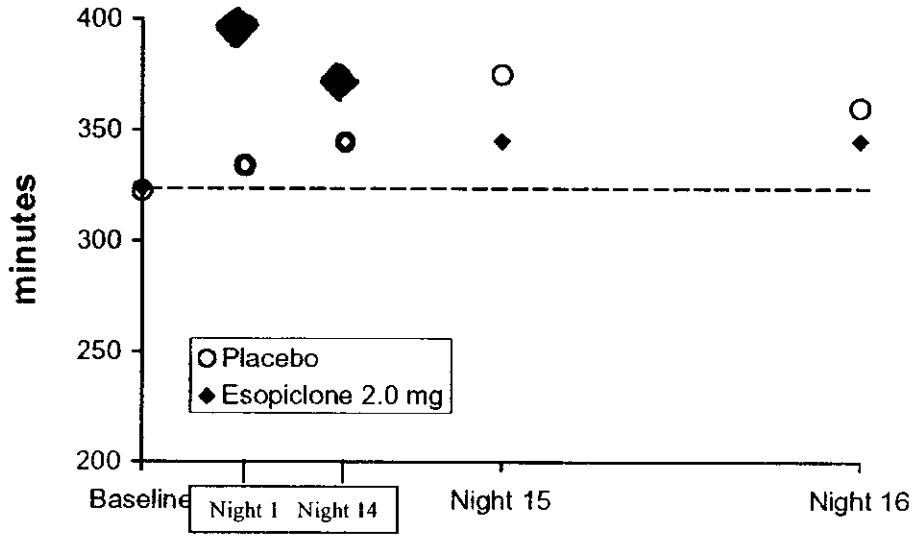


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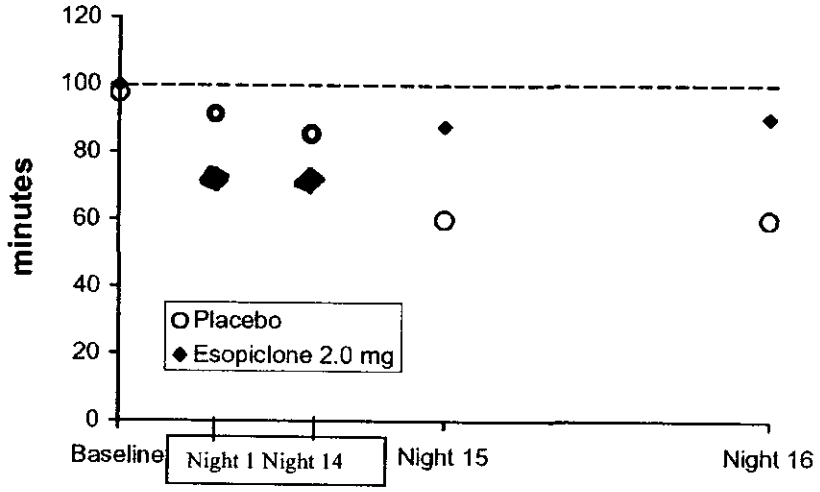
Figure VID4 A -C. Continued. Results on Subjective Sleep Parameters at Baseline, During Treatment (Nights 1 and 14)* and Upon Treatment Cessation (Nights 15 and 16; the 1st and 2nd Nights after Cessation) in the 2-Week Elderly Chronic Insomnia PSG Trial 190-047.

Panel C. Median Subjective WASO*



*** Sponsor's figure was modified to include Double-blind Phase Timepoints (Nights 1 and 14).**

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Table VID8 Study 190-047. Adverse Events After Cessation of Double-blind Treatment.

	Placebo (N=128)	Esopiclone 2 mg (N=136)
BODY SYSTEM	Subjects[1]	Subjects[1]
Preferred Term	n (%)	n (%)
TOTAL	14 (10.9)	22 (16.2)
Body as a Whole	7 (5.5)	13 (9.6)
Accidental Injury	0 (0.0)	4 (2.9)
Asthenia	0 (0.0)	1 (0.7)
Back Pain	0 (0.0)	3 (2.2)
Headache	3 (2.3)	5 (3.7)
Infection	2 (1.6)	1 (0.7)
Injection Site Pain	1 (0.8)	0 (0.0)
Pain	1 (0.8)	4 (2.9)
Cardiovascular System	2 (1.6)	0 (0.0)
Cardiovascular Disorder	1 (0.8)	0 (0.0)
Myocardial Infarction	1 (0.8)	0 (0.0)
Digestive System	1 (0.8)	2 (1.5)
Diarrhea	1 (0.8)	1 (0.7)
Eructation	0 (0.0)	1 (0.7)
Gastrointestinal Hemorrhage	1 (0.8)	0 (0.0)
Nausea	1 (0.8)	0 (0.0)
Vomiting	1 (0.8)	0 (0.0)
Musculoskeletal System	0 (0.0)	2 (1.5)
Arthralgia	0 (0.0)	1 (0.7)
Arthritis	0 (0.0)	1 (0.7)
Nervous System	1 (0.8)	5 (3.7)
Abnormal Dreams	0 (0.0)	1 (0.7)
Anxiety	0 (0.0)	1 (0.7)
Dizziness	0 (0.0)	1 (0.7)
Hypertonia	1 (0.8)	1 (0.7)
Insomnia	0 (0.0)	1 (0.7)
Nervousness	0 (0.0)	1 (0.7)
Somnolence	0 (0.0)	1 (0.7)
Respiratory System	4 (3.1)	2 (1.5)
Bronchitis	1 (0.8)	0 (0.0)
Cough Increased	1 (0.8)	0 (0.0)
Laryngitis	1 (0.8)	0 (0.0)
Pharyngitis	1 (0.8)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.7)
Rhinitis	1 (0.8)	1 (0.7)
Skin and Appendages	1 (0.8)	3 (2.2)
Herpes Simplex	0 (0.0)	1 (0.7)
Pruritis	0 (0.0)	1 (0.7)
Rash	1 (0.8)	1 (0.7)

Note: Study 190-047 was included.
[1] Subjects were counted only once within each body system and each preferred term.
Note: All new adverse events occurring after discontinuation of the double-blind treatment (i.e., between 24 and 72 hours after administration of the last double-blind dose) were presented. For each subject, an adverse event was considered a new event if the subject had not experienced the event during the double-blind period or the event worsened in severity after the end of the double-blind period.
Reference: EOT Table 23.4.2

Table VIE1. Study Schedule for Study 190-026

Observation and Procedure	Screening	Dosing Visit		
Timing	**-14 to 0 days**	**Pre-dose**	**Dosing**	**Post-dose**
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X		
Medical History	X	X[b]		
Heel-to-Toe Gait Test	X			X
Romberg Test	X			X
DSST		X		X
Sleep History	X			
Concomitant Medications	X	X		X
Clinical Laboratory Tests	X			X[c]
Vital Signs	X	X		X[c]
Physical Examination Including Brief Neurological Exam	X	X		X[c]
Hepatitis B & C Test	X			
Pregnancy Test	X (Plasma)	X (Urine)		
Urine Cotinine	X	X		
Urine Drug Screen	X	X		
12-lead ECG	X			X[c]
Study Medication			X	
Drug Administration Record			X	
PSG Recording			X	
Morning Questionnaire	X[a]			X
Aes	X	X	X	X[c]
Plasma Sample for (S)-Zopiclone Analysis	X			X[c]
End-of-Study Assessment				X[c]

[a] A Morning Questionnaire was completed for at least five consecutive days preceding and including the morning of the dosing visit.
[b] Medical history since screening was updated.
[c] Completed by subjects who prematurely discontinued.

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Table VIIA1. Study Schedule for Studies 190-024 and 190-025

Procedure	V1	V2 to V5							
		Day 1			Day 2				
	Screen	Baseline	60 min predose	0 min predose	8.5 h postdose	9 h postdose	9.5 h postdose	12.5 h postdose	16 h postdose
Informed consent	X								
Screening criteria	X	X							
Medical history	X								
Psychiatric history	X								
Sleep history	X	X							
Physical exam	X	X[a]							X[b]
Neurological exam	X	X[a]							X[b]
Heel-to-toe gait test	X	X[a]							X[b]
12-lead ECG	X	X[a]							X[b]
Clinical labs	X	X[a]							X[b]
Hepatitis B and C tests	X								
Pregnancy testing[c]	Serum	Urine							Urine
Urine drug screen	X	X							
Urine cotinine	X	X							
Dose				X					
Awaken					X				
Vital signs	X	X							X[b]
Concomitant meds	X	X							
Adverse events		X	X			X		X	X
Breakfast						X			
CDR training session	X								
CDR assessment			X				X	X	
DSST							X	X	
Clinic discharge									X

[a] Assessment performed at Visit 2 only.
[b] Assessment performed on Day 2 of Visit 5 only.
[c] Serum pregnancy testing performed for all female subjects. Urine pregnancy testing performed for all females of childbearing potential at Day 1 of Visits 2 through 5, Day 2 of Visit 5, and early termination.

Table VIIA2. CDR Assessments in Studies 190-024 and 190-025

Task	Major Measure	Supportive Measure
Attentional Tasks		
Simple Reaction Time	Speed (ms)	
Digit Vigilance Task	Speed of Detections (ms) Percentage of targets detected	False Alarms
Choice Reaction Time	Speed (ms)	Accuracy (%)
Dual Attention Task	Speed of visual target detections (ms) Speed of auditory target detections (ms) Percentage of visual targets detected Percentage of auditory targets detected	False Alarms
Working Memory Tasks		
Numeric Working Memory	Numeric Working Memory sensitivity (SI) Numeric Working Memory speed (ms)	
Spatial Working Memory	Spatial Memory sensitivity (SI) Spatial Memory speed (ms)	
Episodic Secondary Memory		
Immediate Word Recall	Percentage of words recalled	Errors, intrusions
Delayed Word Recall	Percentage of words recalled	Errors, intrusions
Word Recognition	Recognition sensitivity (SI) Recognition speed (ms)	
Picture Recognition	Recognition sensitivity (SI) Recognition speed (ms)	
Motor Control		
Tracking	Average distance from target (mm)	

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Table VIIA3. Studies 190-024 and 190-025. A Description of Each CDR Assessment

Immediate Word Recall

A list of 15 words was presented on the monitor at the rate of 1 every 2 seconds for the subject to remember. The subject was then given 1 minute to recall as many of the words as possible.

Picture Presentation

A series of 20 pictures was presented on the monitor at the rate of 1 every 3 seconds for the subject to remember.

Simple Reaction Time

The subject was instructed to press the 'YES' response button as quickly as possible every time the word 'YES' is presented on the monitor. Fifty stimuli were presented with a varying interstimulus interval.

Digit Vigilance Task

A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was then presented in the center of the screen at the rate of 150 per minute, and the subject was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit. There were 45 targets, and the task lasted for 3 minutes.

Choice Reaction Time

Either the word 'NO' or the word 'YES' was presented on the monitor, and the subject was instructed to press the corresponding button as quickly as possible. There were 50 trials for which each stimulus word was randomly chosen with equal probability, and there was a varying interstimulus interval.

Tracking

The subject used a joystick to track a randomly moving target on the screen for one minute. The average distance off-target per second was recorded.

Spatial Working Memory

A picture of a house was presented on the screen with four of the nine windows lit. The subject had to memorize the position of the lit windows. For each of the 36 subsequent presentations of the house, the subject was required to decide whether or not the one window that was lit was also lit in the original presentation. The subject recorded his or her response by pressing the 'YES' or 'NO' response button as appropriate.

Continued on next page.

Table VIIA3, continued. Studies 190-024 and 190-025. A Description of Each CDR Assessment

Numeric Working Memory

A series of five digits was presented for the subject to hold in memory. This was followed by a series of 30 probe digits for each of which the subject had to decide whether or not it was in the original series and press the 'YES' or 'NO' response button as appropriate. This procedure was repeated twice, using two different series and probes.

Delayed Word Recall

The subject was again given 1 minute to recall as many of the words as possible.

Word Recognition

The original words plus 15 distracter words were presented one at a time in a randomized order. For each word, the subject was required to indicate whether or not he or she recognized it as being from the original list of words by pressing the 'YES' or 'NO' button as appropriate.

Picture Recognition

The original pictures plus 20 distracter pictures were presented one at a time in a randomized order. For each picture, the subject had to indicate whether or not he or she recognized it as being from the original series by pressing the 'YES' or 'NO' button as appropriate.

Dual Attention Task

A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was then presented in the center of the screen at the rate of 150 per minute, and the volunteer was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit. Throughout the task, short auditory tones were played at random intervals. The volunteer was required to press the 'NO' button as quickly as possible every time the tone sounds. There were 150 visual targets and 80 auditory targets. The task lasted 10 minutes.

Training on the CDR system took place prior to dosing in order to ensure an optimal level of performance for the baseline assessment on the first study day. Training helped the subjects to overcome initial test anxiety, familiarize them with the procedures, enable the development of strategies for task performance, and overcome any initial practice effects. Four training sessions were completed by each subject prior to dosing.

Table VIIA4. Studies 190-024 and 190-025. Composite Measures from CDR Assessments

Power of Attention

Power of Attention is the ability to focus attention intensively on a particular task. It was defined as the sum of Simple Reaction Time, Choice Reaction Time, and Digit Vigilance Detection Speed scores.

Speed of Memory Index

Speed of Memory is the speed at which the subjects are able to identify whether or not something is being held in memory. It was defined as the sum of Picture Recognition Speed, Word Recognition Speed, Numeric Working Memory Speed, and Spatial Working Memory Speed.

Quality of Working Memory

Quality of Working Memory is the ability to retain information in memory for very short periods of time to facilitate ongoing activities. It was defined as the sum of the Sensitivity Indices for Numeric Working Memory and Spatial Working Memory.

Quality of Secondary Memory

Quality of Secondary Memory (QSM) is the ability to hold and retrieve verbal and pictorial information from secondary memory. It was based on Immediate Work Recall Accuracy, Delayed Word Recall Accuracy, Word Recognition Accuracy, and Picture Recognition Accuracy and computed according to the following:

QSM = IRCLACC – 6.67 x IRCLINT – 6.67 x IRCLERR + DRCLACC – 6.67 x DRCLINT – 6.67 x DRCLERR + DRECOACC + DRECNACC – 100 + DPICOACC + DPICNACC – 100

continued on the next page.

Table VIIA4, continued. Studies 190-024 and 190-025. Composite Measures from CDR Assessments

where, IRCLACC = Immediate word recall – Percentage of words correctly recalled
IRCLINT = Immediate word recall intrusions – Number of words offered but from previous lists
IRCLERR = Immediate word recall errors – Number of words offered not from this or any previous list
DRLACC = Delayed word recall accuracy – Percentage of words correctly recalled
DRCLINT = Delayed word recall intrusions – Number of words offered but from previous lists
DRCLERR = Delayed word recall errors – Number of words offered not from this or any previous list
DRECOACC = Word recognition – Percentage of original words correctly identified
DRECNACC = Word recognition – Percentage of novel words correctly identified
DPICOACC = Word recognition – Percentage of original pictures correctly identified
DPICNACC = Word recognition – Percentage of novel pictures correctly identified

Continuity of Attention

Continuity of Attention (CA) is the ability to sustain concentration on a single task over a period of time. This measure was based on Digit Vigilance Detection Accuracy (DVDA), Choice Reaction Time Accuracy (CRTA), Digit Vigilance False Alarms (DVFA), and Tracking Error (TE) and computed according to the following:

$$CA = 0.45 \times DVDA + 0.50 \times CRTA - DVFA - TE$$

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Table VIIA6 Demographic Features.

Study 190-024

Age	Mean (SD) Min, max	38.8 (7.7) 28, 53
Gender (n, %)	Male Female	6 (50.0) 6 (50.0)
Race (n, %)	Caucasian Black Asian Hispanic Other	9 (75.0) 3 (25.0) --- --- ---
Height (cm)	Mean (SD) Min, max	170.2 (8.3) 153, 182
Weight (kg)	Mean (SD) Min, max	71.4 (11.2) 57, 92
BMI (kg/m^2)	Mean (SD) Min, max	24.6 (3.1) 18, 28

Reference: Table 14.1.2.

Study 190-025

Age	Mean (SD) Min, max	46.3 (12.4) 28, 64
Gender (n, %)	Male Female	4 (30.8) 9 (69.2)
Race (n, %)	Caucasian Black Asian Hispanic Other	13 (100.0) --- --- --- ---
Height (cm)	Mean (SD) Min, max	164.3 (13.0) 144, 187
Weight (kg)	Mean (SD) Min, max	72.1 (13.6) 54, 101
BMI (kg/m^2)	Mean (SD) Min, max	26.6 (2.5) 22, 30

Reference: Table 14.1.2.

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Table VIIA7. Results of Study 190-024.

Power of Attention (ms) at 9.5 hours Post-Dose.

	Placebo (N=12)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Baseline Mean (SD) Min, max	1065 (86)	1038 (107)	1055 (99)	1064 (92)
Postdose Mean (SD) Min, max	1067 (90)	1083 (97)	1106 (105)	1097 (83)
Change from baseline LS mean (SE) P-value vs placebo	5.2 (18.7) ---	38.4 (18.8) 0.183	51.0 (18.6) 0.068	35.8 (18.6) 0.214

Note: Baseline was defined as the last available predose value at each treatment visit.
References (located in the CDR report in Appendix 16.1.13): Table 14.2.4.1 in Appendix VII of the CDR report; Table 14.2.5.1 in Appendix VIII of the CDR report.

Speed of Memory and Associated CDR Tasks

Timepoint	Placebo (N=12)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Speed of Memory (ms)				
Baseline Mean (SD)	3023 (688)	2939 (654)	2932 (643)	3070 (632)
9.5 hours postdose Mean (SD) Min, max LS mean change (SE) P-value vs placebo	2997 (606) -30.9 (93.5) ---	3196 (769) 255.8 (93.6) 0.023	3214 (740) 261.6 (93.5) 0.021	3443 (999) 374.7 (93.8) 0.002
12.5 hours postdose Mean (SD) Min, max LS mean change (SE) P-value vs placebo	2952 (631) -70.3 (88.9) ---	3076 (843) 134.6 (89.1) 0.085	3060 (637) 105.9 (89.0) 0.136	3456 (796) 389.4 (89.3) <0.001
Picture Recognition—Speed (ms)				
Baseline Mean (SD)	933.7 (322.6)	851.4 (223.0)	875.9 (241.5)	924.6 (232.6)
9.5 hours postdose Mean change (SD)	-37.4 (163.0)	101.6 (125.6)	117.5 (186.9)	165.3 (154.8)
12.5 hours postdose Mean change (SD)	-17.3 (147.2)	66.6 (90.5)	26.8 (114.1)	110.6 (156.0)
Word Recognition—Speed (ms)				
Baseline Mean (SD)	748.0 (138.6)	767.6 (183.9)	794.2 (226.6)	743.4 (126.2)
9.5 hours postdose Mean change (SD)	9.8 (117.7)	68.0 (177.5)	28.7 (144.1)	186.8 (428.1)
12.5 hours postdose Mean change (SD)	-10.1 (103.6)	28.1 (97.5)	-52.0 (205.9)	189.4 (326.1)
Numeric Working Memory—Speed (ms)				
Baseline Mean (SD)	630.1 (139.7)	612.5 (137.9)	609.0 (99.8)	626.5 (106.2)
9.5 hours postdose Mean change (SD)	6.4 (74.8)	23.5 (82.8)	1.8 (61.3)	20.6 (57.2)
12.5 hours postdose Mean change (SD)	-25.5 (62.5)	-5.0 (45.4)	0.6 (54.7)	52.7 (99.7)
Spatial Working Memory—Speed (ms)				
Baseline Mean (SD)	711.3 (205.5)	707.4 (224.5)	672.5 (172.0)	775.7 (364.9)
9.5 hours postdose Mean change (SD)	-10.3 (106.4)	64.1 (127.2)	114.7 (196.0)	0.5 (110.4)
12.5 hours postdose Mean change (SD)	-18.9 (105.6)	47.9 (248.1)	132.7 (216.5)	32.9 (221.1)

Note: Baseline was defined as the last available predose value at each treatment visit.
References (located in the CDR report in Appendix 16.1.13): Tables 14.2.4.2, 14.2.4.16, 14.2.4.18, 14.2.4.22, and 14.2.4.24 in Appendix VII of the CDR report; Table 14.2.5.2.1 in Appendix VIII of the CDR report.

Table VIIA8. Study 190-024. Quality of Working Memory, Secondary Memory, and Continuity of Attention

Timepoint	Placebo (N=12)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Quality of Working Memory (SI)				
Baseline				
Mean (SD)	1.89 (0.07)	1.83 (0.12)	1.85 (0.14)	1.80 (0.30)
9.5 hours postdose				
Mean (SD)	1.81 (0.20)	1.84 (0.14)	1.80 (0.21)	1.81 (0.15)
Min, max				
LS mean change (SE)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
P-value vs placebo	---	0.450	0.937	0.672
12.5 hours postdose				
Mean (SD)	1.82 (0.22)	1.86 (0.10)	1.76 (0.25)	1.82 (0.11)
Min, max				
LS mean change (SE)	0.0 (0.0)	0.0 (0.0)	-0.1 (0.0)	0.0 (0.0)
P-value vs placebo	---	0.234	0.467	0.426
Quality of Secondary Memory (#)				
Baseline				
Mean (SD)	216.0 (53.9)	198.2 (41.7)	213.2 (50.4)	198.3 (44.0)
9.5 hours postdose				
Mean (SD)	185.6 (43.0)	187.1 (45.9)	184.6 (44.6)	178.1 (34.9)
Min, max				
LS mean change (SE)	-25.0 (11.0)	-15.8 (11.0)	-24.8 (11.0)	-24.9 (11.0)
P-value vs placebo	---	0.497	0.986	0.992
12.5 hours postdose				
Mean (SD)	171.4 (52.2)	185.4 (46.4)	190.6 (54.3)	164.3 (43.3)
Min, max				
LS mean change (SE)	-38.4 (13.8)	-18.1 (13.8)	-18.2 (13.8)	-39.3 (13.8)
P-value vs placebo	---	0.243	0.238	0.959
Continuity of Attention (#)				
Baseline				
Mean (SD)	61.9 (7.0)	55.9 (22.9)	63.2 (3.5)	63.1 (3.8)
9.5 hours postdose				
Mean (SD)	62.7 (3.2)	51.5 (31.3)	61.0 (5.5)	62.2 (4.5)
Min, max				
LS mean change (SE)	0.7 (2.1)	-3.5 (2.1)	-2.5 (2.1)	-1.3 (2.1)
P-value vs placebo	---	0.090	0.186	0.412
12.5 hours postdose				
Mean (SD)	61.3 (3.5)	56.3 (13.6)	61.0 (4.5)	61.7 (5.2)
Min, max				
LS mean change (SE)	-0.1 (1.4)	-2.3 (1.4)	-1.0 (1.4)	-0.3 (1.4)
P-value vs placebo	---	0.238	0.619	0.903

Note: Baseline was defined as the last available predose value at each treatment visit.
References (located in the CDR report in Appendix 16.1.13): Tables 14.2.4.3 to 14.2.4.5 in Appendix VII of the CDR report; Tables 14.2.5.3.1, 14.2.5.4, and 14.2.5.5.1 in Appendix VIII of the CDR report.

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Table VIIA9. Study 190-024 DSST Results.

Timepoint	Placebo (N=12)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Baseline				
Mean (SD)	62.7 (12.2)	64.2 (10.3)	61.6 (9.8)	62.3 (13.9)
Min, max	42.0, 76.0	40.0, 77.0	41.0, 72.0	38.0, 84.0
9.5 hours postdose				
Mean (SD)	62.0 (13.6)	63.0 (10.6)	62.3 (12.8)	59.7 (10.2)
Min, max				
LS mean change (SE)	-0.7 (1.8)	-0.8 (1.8)	0.5 (1.8)	-2.8 (1.8)
P-value vs placebo	---	0.950	0.614	0.368
12 hours postdose				
Mean (SD)	64.3 (12.8)	62.9 (11.8)	63.0 (11.8)	61.8 (12.0)
Min, max				
LS mean change (SE)	1.7 (1.7)	-1.2 (1.7)	1.3 (1.7)	-0.6 (1.7)
P-value vs placebo	---	0.250	0.894	0.351

Note: Baseline was defined as the last available predose value at each treatment visit.
References (located in the CDR report in Appendix 16.1.13): Table 14.2.4.6 in Appendix VII of the CDR report; Table 14.2.5.6 in Appendix VIII of the CDR report.

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Table VIIA10. Panels A-B. Results in Study 190-025.

Panel A. Power of Attention Results

	Placebo (N=13)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Baseline				
Mean (SD)	1140 (122)	1132 (118)	1132 (106)	1136 (126)
Min, max				
Postdose				
Mean (SD)	1186 (116)	1162 (127)	1161 (112)	1187 (125)
Min, max				
Change from baseline				
LS mean (SE)	48.4 (17.5)	28.8 (18.0)	28.0 (18.0)	50.8 (18.0)
P-value vs placebo	---	0.348	0.328	0.910

Note: Baseline was defined as the last available predose value at each treatment visit.
References: (located in the CDR Report in Appendix 16.1.13): Table 14.2.4.1 in Appendix VII of the CDR report:

Panel B. Quality of Secondary Memory and Associated CDR Tasks

Timepoint	Placebo (N=13)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Quality of Secondary Memory (#)				
Baseline				
Mean (SD)	154.2 (70.4)	155.6 (57.4)	151.9 (70.0)	159.9 (74.0)
9.5 hours postdose				
Mean (SD)	146.4 (57.3)	154.4 (63.1)	131.3 (49.0)	123.7 (57.8)
Min, max				
LS mean change (SE)	-10.2 (12.0)	-2.1 (12.3)	-23.5 (12.3)	-34.9 (12.3)
P-value vs placebo	---	0.560	0.344	0.084
12.5 hours postdose				
Mean (SD)	145.8 (61.0)	144.0 (82.6)	116.1 (66.8)	132.6 (54.2)
Min, max				
LS mean change (SE)	-9.7 (18.0)	-13.0 (18.3)	-40.4 (18.3)	-25.0 (18.3)
P-value vs placebo	---	0.810	0.031	0.266
Immediate Word Recall—Accuracy (%)				
Baseline				
Mean (SD)	35.4 (16.4)	32.8 (15.4)	33.1 (17.1)	35.6 (19.0)
9.5 hours postdose				
Mean change (SD)	-3.8 (14.5)	5.3 (15.9)	-4.2 (9.1)	-9.2 (17.3)
12.5 hours postdose				
Mean change (SD)	-1.3 (11.4)	-2.0 (14.9)	-6.1 (14.3)	-4.7 (10.2)
Delayed Word Recall—Accuracy (%)				
Baseline				
Mean (SD)	26.9 (16.2)	23.3 (18.0)	25.3 (18.8)	25.3 (18.4)
9.5 hours postdose				
Mean change (SD)	-4.6 (14.9)	2.8 (14.6)	-3.9 (11.4)	-6.4 (17.3)
12.5 hours postdose				
Mean change (SD)	1.8 (9.6)	1.9 (16.5)	-3.9 (15.5)	-4.2 (15.0)
Word Recognition—Accuracy (SI)				
Baseline				
Mean (SD)	0.46 (0.17)	0.55 (0.22)	0.52 (0.17)	0.47 (0.27)
9.5 hours postdose				
Mean change (SD)	0.02 (0.22)	-0.07 (0.27)	-0.18 (0.31)	0.04 (0.24)
12.5 hours postdose				
Mean change (SD)	-0.02 (0.22)	-0.11 (0.31)	-0.17 (0.32)	-0.06 (0.27)
Picture Recognition—Accuracy (SI)				
Baseline				
Mean (SD)	0.60 (0.21)	0.61 (0.20)	0.60 (0.23)	0.64 (0.23)
9.5 hours postdose				
Mean change (SD)	-0.02 (0.17)	-0.09 (0.13)	-0.10 (0.18)	-0.15 (0.28)
12.5 hours postdose				
Mean change (SD)	-0.08 (0.18)	-0.02 (0.17)	-0.08 (0.16)	-0.05 (0.24)

Note: Baseline was defined as the last available predose value at each treatment visit.
References: (located in the CDR Report in Appendix 16.1.13): Tables 14.2.4.4, 14.2.4.19, 14.2.4.20, 14.2.4.21, and 14.2.4.23 in Appendix VII of the CDR report: Table 14.2.5.4 in Appendix VIII of the CDR report.

Table VIIA11. Study 190-025 Results.
Speed of Memory, Quality of Working Memory, and Continuity of Attention

Timepoint	Placebo (N=13)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Speed of Memory (ms)				
Baseline				
Mean (SD)	3464 (671)	3545 (712)	3467 (673)	3412 (755)
9.5 hours postdose				
Mean (SD)	3469 (842)	3794 (987)	3672 (606)	3637 (700)
Min, max				
LS mean change (SE)	2.2 (115.3)	246.7 (119.7)	204.5 (119.5)	227.2 (119.6)
P-value vs placebo	---	0.150	0.231	0.183
12.5 hours postdose				
Mean (SD)	3421 (926)	3550 (723)	3542 (709)	3645 (700)
Min, max				
LS mean change (SE)	-47.5 (103.6)	5.6 (107.6)	74.6 (107.4)	232.9 (107.5)
P-value vs placebo	---	0.724	0.418	0.068
Quality of Working Memory (SI)				
Baseline				
Mean (SD)	1.70 (0.28)	1.69 (0.30)	1.64 (0.35)	1.70 (0.29)
9.5 hours postdose				
Mean (SD)	1.67 (0.26)	1.64 (0.31)	1.66 (0.35)	1.63 (0.31)
Min, max				
LS mean change (SE)	-0.02 (0.07)	-0.04 (0.08)	0.00 (0.08)	-0.05 (0.08)
P-value vs placebo	---	0.790	0.807	0.693
12.5 hours postdose				
Mean (SD)	1.59 (0.34)	1.67 (0.43)	1.73 (0.19)	1.65 (0.28)
Min, max				
LS mean change (SE)	-0.12 (0.08)	-0.02 (0.08)	0.07 (0.08)	-0.05 (0.08)
P-value vs placebo	---	0.417	0.118	0.545
Continuity of Attention (#)				
Baseline				
Mean (SD)	54.1 (14.9)	44.5 (29.3)	54.9 (28.3)	53.8 (14.2)
9.5 hours postdose				
Mean (SD)	56.7 (9.4)	48.8 (23.1)	55.3 (11.7)	52.8 (14.8)
Min, max				
LS mean change (SE)	4.6 (3.1)	-1.1 (3.2)	2.6 (3.2)	0.5 (3.2)
P-value vs placebo	---	0.116	0.572	0.238
12.5 hours postdose				
Mean (SD)	54.3 (9.3)	48.7 (20.1)	55.7 (10.8)	50.8 (15.0)
Min, max				
LS mean change (SE)	1.4 (2.9)	-0.5 (3.1)	2.8 (3.0)	-1.7 (3.0)
P-value vs placebo	---	0.652	0.747	0.463

Note: Baseline was defined as the last available predose value at each treatment visit.
References: (located in the CDR Report in Appendix 16.1.13): Tables 14.2.4.2, 14.2.4.3, and 14.2.4.5 in Appendix VII of the CDR report; Tables 14.2.5.2.1, 14.2.5.3.1, and 14.2.5.5.1 in Appendix VIII of the CDR report.

Table VIIA12. Study 190-025. DSST Results

Timepoint	Placebo (N=13)	Esopiclone 2 mg (N=12)	Esopiclone 3 mg (N=12)	Flurazepam 30 mg (N=12)
Baseline				
Mean (SD)	62.8 (11.2)	57.8 (16.8)	59.1 (12.6)	58.4 (13.0)
Min, max		—		
9.5 hours postdose				
Mean (SD)	59.9 (13.3)	61.6 (13.2)	57.6 (12.4)	59.3 (10.5)
Min, max		—		
LS mean change (SE)	-1.6 (1.9)	3.2 (1.9)	-1.6 (1.9)	0.6 (1.9)
P-value vs placebo	---	0.074	0.999	0.405
12 hours postdose				
Mean (SD)	63.8 (12.4)	58.1 (20.3)	59.0 (13.0)	56.6 (18.1)
Min, max		—		
LS mean change (SE)	0.6 (2.7)	0.4 (2.8)	-0.1 (2.8)	-1.8 (2.8)
P-value vs placebo	---	0.949	0.862	0.539

Note: Baseline was defined as the last available predose value at each treatment visit.
References: (located in the CDR Report in Appendix 16.1.13): Table 14.2.4.6 in Appendix VII of the CDR report; Table 14.2.5.6 in Appendix VIII of the CDR report.

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Table VIIB1 Panels A and B. Study 190-012 Respiratory Parameter Results

Panel A. Results on the Adjusted Mean of the Slope of the Ventilatory Response to C02 Partial Pressure.

Time Point	Treatment	Adjusted Mean Slope	SD	Estimated Difference*	95% Confidence Interval	P-value
2 Hour	Placebo	3.32	1.50			
	Codeine Sulfate 60 mg	2.83	0.86	-0.49	(-0.96,-0.02)	0.0398
	(S)-Zopiclone 3.0 mg	3.40	1.19	0.07	(-0.40, 0.55)	0.7549
	(S)-Zopiclone 7.0 mg	3.27	1.41	-0.05	(-0.53, 0.43)	0.8361
4 Hour	Placebo	2.86	0.80			
	Codeine Sulfate 60 mg	3.08	1.25	0.22	(-0.33, 0.76)	0.4267
	(S)-Zopiclone 3.0 mg	2.92	1.22	0.05	(-0.50, 0.61)	0.8454
	(S)-Zopiclone 7.0 mg	3.10	1.40	0.24	(-0.31, 0.79)	0.3864
6 Hour	Placebo	2.75	0.82			
	Codeine Sulfate 60 mg	2.83	1.09	0.08	(-0.43, 0.60)	0.7498
	(S)-Zopiclone 3.0 mg	2.98	1.21	0.23	(-0.29, 0.76)	0.3704
	(S)-Zopiclone 7.0 mg	2.96	0.90	0.21	(-0.31, 0.74)	0.4134

Note: The fitted model is SLOPE = SEQUENCE + SUBJECT(SEQUENCE) + PERIOD + TREATMENT + COVARIATE where the covariate is the 45-minute pre-dose measurement of the corresponding primary outcome measure (slope) and SUBJECT(SEQUENCE) is a random term.
*Estimated difference is the difference between the treatment and placebo (Treatment - Placebo).
Reference: Table 14.2.1.

Panel B. Results on the Adjusted Mean of the Slope of the Mouth Occlusion Pressure Response to C02 Partial Pressure Change.

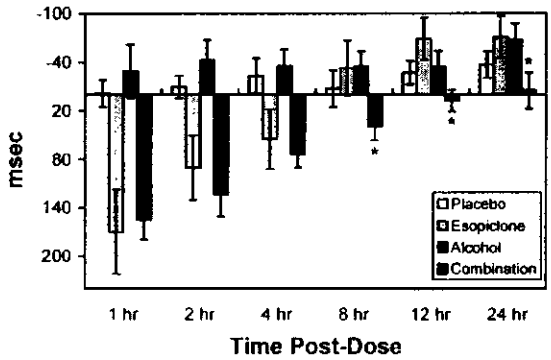
Time Point	Treatment	Adjusted Mean Slope	SD	Estimated Difference*	95% Confidence Interval	P-value
2 Hour	Placebo	1.19	0.62			
	Codeine Sulfate 60 mg	0.92	0.30	-0.27	(-0.58, 0.04)	0.0866
	(S)-Zopiclone 3.0 mg	1.01	0.55	-0.18	(-0.50, 0.15)	0.2784
	(S)-Zopiclone 7.0 mg	0.96	0.60	-0.23	(-0.55, 0.09)	0.1531
4 Hour	Placebo	1.02	0.40			
	Codeine Sulfate 60 mg	1.18	0.41	0.16	(-0.10, 0.41)	0.2218
	(S)-Zopiclone 3.0 mg	0.90	0.50	-0.12	(-0.39, 0.14)	0.3509
	(S)-Zopiclone 7.0 mg	1.03	0.61	0.01	(-0.25, 0.28)	0.9171
6 Hour	Placebo	1.13	0.38			
	Codeine Sulfate 60 mg	1.02	0.42	-0.11	(-0.32, 0.10)	0.2777
	(S)-Zopiclone 3.0 mg	0.88	0.32	-0.25	(-0.47,-0.03)	0.0256
	(S)-Zopiclone 7.0 mg	0.93	0.43	-0.20	(-0.41, 0.02)	0.0733

Note: The fitted model is SLOPE = SEQUENCE + SUBJECT(SEQUENCE) + PERIOD + TREATMENT + COVARIATE where the covariate is the 45-minute pre-dose measurement of the corresponding primary outcome measure (slope) and SUBJECT(SEQUENCE) is a random term.
*Estimated difference is the difference between the treatment and placebo (Treatment - Placebo).
Reference: Table 14.2.1.

Figure VIIC1. Panels A-H. Study 190-015. Results of Psychometric Parameters Showing Significantly Greater Effects on Performance after ESZ-Alcohol Combination Treatment compared to Other Mono-Drug or Placebo Treatment Conditions

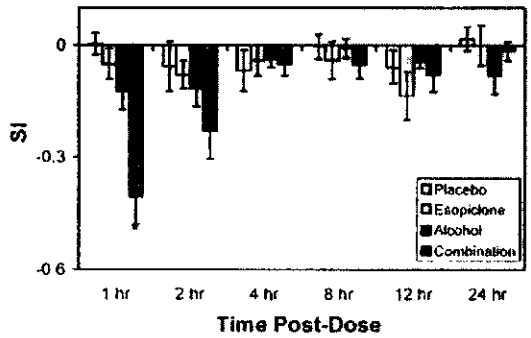
Panel A.

Numeric Working Memory - Speed



Panel B.

Spatial Working Memory - Sensitivity Index



Panel C.

Immediate Word Recall - % Words Recalled

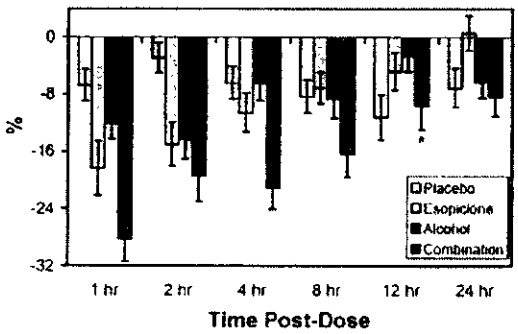
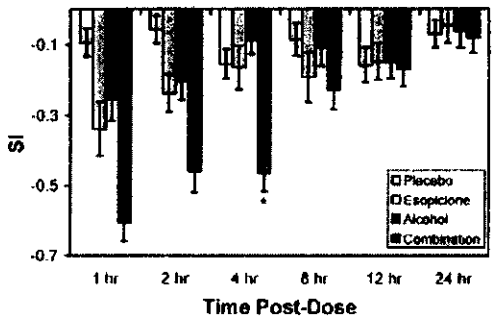


Figure VIIC1 Panels A-H, continued.
Study 190-015. Results of Psychometric Parameters Showing Significantly Greater Effects on Performance after ESZ-Alcohol Combination Treatment compared to Other Mono-Drug or Placebo Treatment Conditions

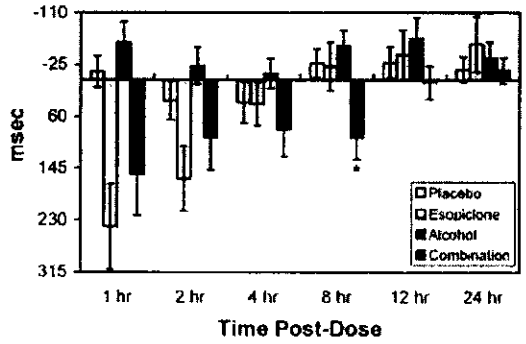
Panel D.

Word Recognition - Sensitivity Index



Panel E.

Picture Recognition - Speed



Panel F.

Power of Attention

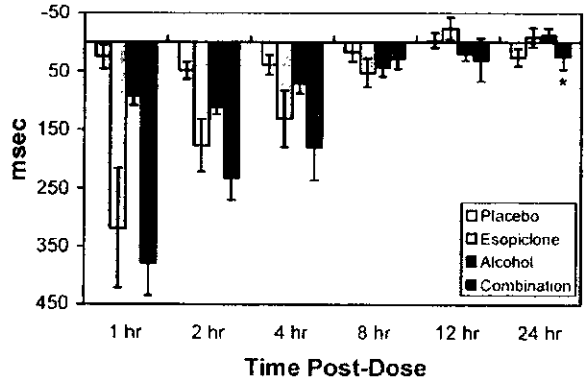
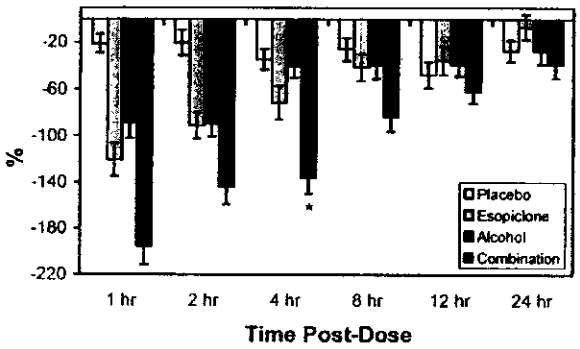


Figure VIIC Panels A-H, continued.
Study 190-015. Results of Psychometric Parameters Showing Significantly Greater Effects on Performance after ESZ-Alcohol Combination Treatment compared to Other Mono-Drug or Placebo Treatment Conditions

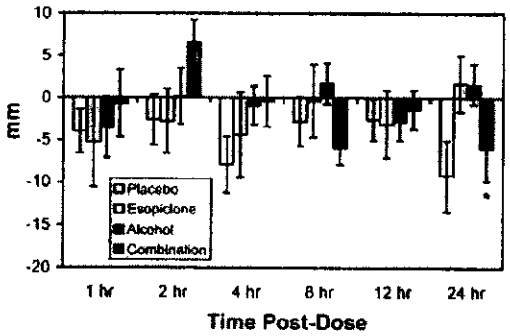
Panel G.

Quality of Secondary Memory



Panel H.

Self-Rated Calmness



*P<0.05 based on statistical analysis of the estimates. Graphs depict mean changes from baseline. Error bars represent standard deviations.
Reference: Appendix 16.1.13 (CDR Report, Appendices II and III)

Table VIII.A1. Enumeration of Subjects for All Studies and in Each Integrated Study Type Category (Safety Population), as provided by the sponsor.

Study Type	Placebo (N=812)	Eszopiclone					
		1 mg (N=234)	2 mg (N=555)	2.5 mg (N=71)	3 mg (N=1019)	≥3.5 mg (N=187)	All Active (N=1839)
Study Number	n	n	n	n	n	n	n
Daytime (1-7 days) studies in healthy volunteers	124	24	52	6	135	91	295
190-001	34	6	6	6	6	22	46
190-002*	12	12			12	12	36
190-005	12	6	6		6	6	24
190-010*						16	16
190-011*			40		39		79
190-012*	13				13	13	13
190-015*[a]	24					22	22
190-018[a]	10				10		10
190-019[a]	9				9		9
190-020[a]	10				10		10
190-021*[a]					12		12
190-023*[a]					18		18
Nighttime, (1-7 days) studies in non-elderly adult healthy volunteers	110	47	109		110	96	350
190-024*	12		12		12		12
190-026	98	47	97		98	96	338
Nighttime, (1-7 days) studies in non-elderly adult subjects with insomnia	76	63	75	65	76		77
190-025*	13		12		12		12
190-045*	63	63	63	65	64		65
Nighttime, 2-week studies in elderly subjects with insomnia	208	100	215	0	0	0	315
190-047[b]	128	28	136	0	0	0	164
190-048	80	72	79				151
Nighttime, 6-week study in non-elderly adult subjects with insomnia	99		104		105		209
190-046	99		104		105		209
Nighttime, long-term (6-month double-blind) study in non-elderly adult subjects with insomnia	195	0	0	0	593	0	593
190-049	195	0	0	0	593	0	593

* Cross-over studies are denoted with an asterisk.
[a] Combination data are not integrated in the ISS.
[b] Subjects from Study 190-047 who received 1.5 mg esopiclone are presented in the 1 mg dose group.
Note: For all studies, each subject contributed only once to the Total and once to each relevant treatment or dose category. For the cross-over studies, however, each subject may have contributed to more than one treatment and/or dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045).
Reference: EOT Table 2.1.

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Table VIII.C.1

Duration of Treatment Category by Average Daily Dose (mg/day) and Study Type (Safety Population)

Study Type / Duration of Treatment	Average Daily Dose (mg/day)					
	Placebo	Eszopiclone				
		≥0.5-1.75 mg[1]	>1.75-2.25 mg	>2.25-2.75 mg	>2.75-3.25 mg	>3.25 mg
Daytime, Short-term (1-7 days) studies in healthy volunteers[2] N	124	24	52	6	122	91
1-7 days n (%)	113 (91.1)	13 (54.2)	52 (100)	6 (100)	110 (90.2)	79 (86.8)
>1-2 weeks n (%)[3]	11 (8.9)	11 (45.8)	0 (0.0)	0 (0.0)	12 (9.8)	12 (13.2)
Nighttime, Short-term (1-7 days) studies in non-elderly adult healthy volunteers (Studies 190-024 and 190-026) N	110	47	97	12	98	96
1-7 days n (%)	110 (100)	47 (100)	97 (100)	12 (100)	98 (100)	96 (100)
Nighttime, Short-term (1-7 days) studies in non-elderly subjects with insomnia (Studies 190-025 and 190-045) N	76	0	63	14	0	0
1-7 days n (%)	76 (100)	0 (0.0)	2 (3.2)	14 (100)	0 (0.0)	0 (0.0)
>1-2 weeks n (%)[4]	0 (0.0)	0 (0.0)	61 (96.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nighttime, 2-week studies in elderly subjects with insomnia (Studies 190-047 and 190-048) n	208	107	207	1	0	0
1-7 days n (%)	13 (6.3)	6 (5.6)	7 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
>1-2 weeks n (%)	128 (61.5)	69 (64.5)	130 (62.8)	1 (100.0)	0 (0.0)	0 (0.0)
>2-4 weeks n (%)[3]	67 (32.2)	32 (29.9)	70 (33.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nighttime, 6-week study in non-elderly adult subjects with insomnia (Study 190-046) N	99	1	103	4	101	0
1-7 days n (%)	1 (1.0)	0 (0.0)	3 (2.9)	0 (0.0)	2 (2.0)	0 (0.0)
>1-2 weeks n (%)	1 (1.0)	1 (100)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
>4-6 weeks n (%)	14 (14.1)	0 (0.0)	13 (12.6)	0 (0.0)	9 (8.9)	0 (0.0)
>6-8 weeks n (%)[3]	83 (83.8)	0 (0.0)	87 (84.5)	3 (75.0)	90 (89.1)	0 (0.0)
Nighttime, Long-term (6-month double-blind study in non-elderly adult subjects with insomnia (Study 190-049) N	187	28	48	102	373	12
1-7 days n (%)	8 (4.3)	0 (0.0)	3 (6.3)	1 (1.0)	5 (1.3)	2 (16.7)
>1-2 weeks n (%)	5 (2.7)	0 (0.0)	0 (0.0)	1 (1.0)	4 (1.1)	1 (8.3)
>2-4 weeks n (%)	13 (7.0)	3 (10.7)	3 (6.3)	8 (7.8)	12 (3.2)	1 (8.3)
>4-6 weeks n (%)	15 (8.0)	3 (10.7)	4 (8.3)	4 (3.9)	20 (5.4)	2 (16.7)
>6-8 weeks n (%)[3]	8 (4.3)	1 (3.6)	3 (6.3)	5 (4.9)	4 (1.1)	1 (8.3)
>8-12 weeks n (%)	10 (5.3)	5 (17.9)	3 (6.3)	8 (7.8)	20 (5.4)	0 (0.0)
>12-16 weeks n (%)	7 (3.7)	1 (3.6)	5 (10.4)	8 (7.8)	19 (5.1)	3 (25.0)
>16-20 weeks n (%)	8 (4.3)	1 (3.6)	3 (6.3)	4 (3.9)	9 (2.4)	0 (0.0)
>20-24 weeks n (%)	3 (1.6)	4 (14.3)	2 (4.2)	2 (2.0)	17 (4.6)	0 (0.0)
>24-28 weeks n (%)	101 (54.0)	10 (35.7)	21 (43.8)	54 (52.9)	256 (68.6)	2 (16.7)
>28-32 weeks n (%)	9 (4.8)	0 (0.0)	1 (2.1)	7 (6.9)	7 (1.9)	0 (0.0)

[1] There were no subjects who received ≤0.5-mg eszopiclone.
[2] Studies 190-001, 190-002, 190-005, 190-010, 190-011, 190-012, 190-015, 190-018, 190-019, 190-020, 190-021, and 190-023 were included.
[3] Subjects were included in a duration category based on the double-blind dosing information, not on the planned study duration.
[4] For Study 190-045, total planned exposure to eszopiclone was 8 days for each subject. The subjects were to receive each of four eszopiclone doses for 2 consecutive days with a wash-out period between each treatment.
Note: Each subject in the following placebo-controlled sequential/cross-over studies contributed once to the placebo group and once to the eszopiclone group: Studies 190-012, 190-015, 190-024, 190-025, and 190-045.
Note: For all sequential/cross-over studies, the average daily dose was calculated from treatment days, excluding any washout period(s).
Note: For some subjects in the long-term safety study 190-049, the drug accountability data were missing. These subjects are therefore excluded from summarization in this table.
Reference: EOT Table 5.2

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Table VIII.E.1

Other Serious Adverse Events for All Integrated Studies (Safety Population)

Treatment	Subject No.	Preferred Term	Reported Term	AE Start Date	Freq	Out	AE End Date	Severity	Rel	Action Taken	AE Treatment	UAE?	IND Safety Report Date and Serial No.
Study 190-047: Nighttime, 2-Week Study in Elderly Subjects with Insomnia													
2 mg ESO	169714	Accidental Injury	Accidental Injury Diffuse Pain	—	Once	Res	—	Moderate	NR	None	Other	No	29Mar2002 (No. 091) 10Apr2002 (No. 093)
PBO	664717	Gastrointestinal Hemorrhage	Lower Gastrointestinal Bleeding	—	Once	Res	—	Severe	NR	None	Surgical	Yes	01Mar2002 (No. 085) 04Apr2002 (No. 092)
PBO	665710	Myocardial Infarction	Acute Non-Q Wave Myocardial Infarction	—	Once	Res	—	Severe	NR	Disc	Other	Yes	06Mar2002 (No. 086) 04Apr2002 (No. 092) 10Apr2002 (No. 093)
Study 190-048: Nighttime, 2-Week Study in Elderly Subjects with Insomnia													
1 mg ESO	427004	Chest Pain	Atypical Chest Pain	—	Inter	Res	—	Moderate	NR	None	Medication	No	31Jul2001 (No. 048) 12Oct2001 (No. 065)
Study 190-049: Nighttime, 6-Month Double-blind Study in Non-Elderly Subjects with Insomnia													
3 mg ESO	0317030	Abdominal Pain	Abdominal Pain		Inter	Res	—	Severe	NR	Intr	Medication	No	15Aug2001 (No. 055)
3 mg ESO	0467013	Accidental Injury	Fracture Left Hand	—	Once	Res	—	Moderate	NR	Intr	Medication	No	06July2001 (No. 042) 17Sep2001 (No. 060)
3 mg ESO	0405003	Accidental Injury	Severe Trauma	—	Once	Ong		Severe	NR	Disc	Surgical	No	03July2001 (No. 041) 07Aug2001 (No. 052) 17Sep2001 (No. 060)
3 mg ESO	0415007	Agitation	Panic Attack	—	Once	Res	—	Severe	NR	Disc	Medication	Yes	03July2001 (No. 041) 15Aug2001 (No. 055) 12Oct2001 (No. 066)
3 mg ESO	0443005	Agitation	Panic Disorder	—	Cont	Res	—	Severe	NR	Disc	Other	Yes	03July2001 (No. 041)
3 mg ESO	0110004	Arthrosis	Worsening DJD Bilateral Knees	—	Cont	Res	—	Severe	NR	None	Surgical	Yes	31July2001 (No. 047) 07Nov2001 (No. 070)
3 mg ESO	0433008	Asthma	Asthma Attack	—	Cont	Res	—	Severe	NR	None	Medication	Yes	21Aug2001 (No. 056) 07Nov2001 (No. 070)
3 mg ESO	0448024	Chest Pain	Atypical Chest Pain	—	Cont	Res	—	Severe	NR	Intr	Other	No	03July2001 (No. 041) 21Aug2001 (No. 056)
3 mg ESO	0439001	Chest Pain	Atypical Chest Pain Syndrome	—	Inter	Res	—	Severe	Poss	Disc	Other	No	21Aug2001 (No. 056) 12Oct2001 (No. 066) 21Nov2001 (No. 071)
3 mg ESO	0317033	Chest Pain	Chest Pain	—	Once	Res	—	Moderate	NR	None	Other	No	12Oct 2001 (No. 066) 29Mar2002 (No. 091)

Continued on the next page.

Table VIII.E.1, continued
Other Serious Adverse Events for All Integrated Studies (Safety Population) (continued)

Treatment	Subject No.	Preferred Term	Reported Term	AE Start Date	Freq	Out	AE End Date	Severity	Rel	Action Taken	AE Treatment	UAE?	IND Safety Report Date and Serial No.
Study 190-049: Nighttime, 6-Month Double-blind Study in Non-Elderly Subjects with Insomnia (continued)													
3 mg ESO	0462002	Cholelithiasis	Cholecystolithiasis	—	Once	Res	—	Moderate	NR	Intr	Surgical	Yes	24Aug2001 (No. 058) 12Oct2001 (No. 066)
3 mg ESO	0317030	Gastrointestinal Disorder	Abdominal Adhesions	—	Inter	Res	—	Severe	NR	Intr	Surgical	Yes	20Sep2001 (No. 061)
3 mg ESO	0439026	Gastrointestinal Disorder	Appendicitis	—	Cont	Res	—	Severe	NR	Intr	Surgical	Yes	03July2001 (No. 041
3 mg ESO	0093025	Gastrointestinal Disorder	Appendicitis (Gangrenous ruptured appendix)	—	Once	Res	—	Severe	NR	Intr	Surgical	Yes	21Dec2001 (No. 079 29Mar2002 (No. 091)
3 mg ESO	0412006	Kidney Calculus	Kidney Stone	—	Inter	Res	—	Severe	NR	Intr	Medication	Yes	01Aug2001 (No. 049) 15Aug2001 (No. 055)
3 mg ESO	0471021	Neurosis	Personal Crisis	—	Cont	Res	—	Severe	NR	Disc	Medication	Yes	07Aug2001 (No. 051)
3 mg ESO	0087013	Overdose	Drug Overdose	—	Unk	Unk	—	Severe	Poss	Disc	Other	Yes	12Apr2001 (No. 035)
3 mg ESO	0409009	Uterine Fibroids Enlarged	Uterine Fibroids	—	Cont	Res	—	Severe	NR	Disc	Surgical	Yes	21Nov2001 (No. 071) 21Feb2002 (No. 081
PBO	0422007	Chest Pain	Chest Pain	—	Inter	Res	—	Moderate	NR	None	Other	No	20Sep2001 (No. 061) 10Apr2002 (No. 093)
PBO	0472011	Gastrointestinal Disorder	Appendicitis	—	Once	Res	—	Severe	NR	None	Surgical	Yes	12 Oct2001 (No. 066)
Study 190-049: SAE Occurred >30 Days Following the Last Dose of Double-blind Treatment													
3 mg ESO	0416001	Accidental Injury	Pulled Muscle Left Chest Wall	—	Cont	Res	—	Severe	NR	None	Medication	No	03July2001 (No. 041)

Eso = Esopiclone; PBO = Placebo; Out = outcome; Freq = Frequency; Cont = Continuous; Inter = Intermittent; Res = resolved; Ong = ongoing; Unk = Unknown; Rel = relationship to treatment; NR = not related; Poss = possibly related; Disc = subject discontinued; Intr = study treatment interrupted. Med = Medication; UAE = Unexpected Adverse Event.

Note: Serious adverse events prior to treatment are not summarized.

Reference: EOT Listing 4.2.1. See CSR 190-049, Appendix 16.2.9.2 for subject 0416001.

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Tables VIII.E.2-3

Other Serious Adverse Events that Occurred During the Open-label Phase of Study 190-049 (Safety Population)

Table VIII.E.2

Double-blind Treatment	Subject No.	Preferred Term	Reported Term	AE Start Date	Freq	Out	AE End Date	Severity	Rel	Action Taken	AE Treatment	UAE?	IND Safety Report Date and Serial No.
Study 190-049: SAEs that Occurred During Open-Label Treatment													
3 mg ESO	0421005	Accidental Injury	Neck and Back Injury		Once	Res		Severe	NR	Disc	Surgical	No	21Nov2001 (No. 071) 15Mar2002 (No. 089)
PBO	0093018	Accidental Injury	Torn Right Rotator Cuff		Once	Res		Moderate	NR	None	Surgical	Yes	27Feb2002 (No. 083) 06May2002 (No. 97)
PBO	0087022	Anemia	Anemia Secondary to Breast Reduction and Tummy Tuck		Cont	Res		Moderate	Inter	Other	None	Yes	22Apr2002 (No. 094)
3 mg ESO	0421002	Atrial Fibrillation	Atrial Fibrillation		Cont	Ong		Severe	NR	Disc	Medication	Yes	07Nov2001 (No. 070)
3 mg ESO	0431014	Chest Pain	Chest Pain		Cont	Res		Moderate	NR	Intr	Other	No	06Mar2002 (No. 086) 04Apr2002 (No. 092)
3 mg ESO	0412018	Chest Pain	Chest Pain		Inter	Res		Severe	NR	Intr	Medication	Yes	24Jun2002 (No. 103) 23Jul2002 (No. 105)
3 mg ESO	0420002	Diabetes Mellitus	New Onset of Diabetes		ont	Ong		Moderate	Poss	None	Medication	Yes	28Feb2002 (No. 084)
PBO	0471011	Joint Disorder	Hip Degeneration		Once	Res		Severe	NR	Inter	Other	Yes	04Apr2002 (No 092) 20May2002 (No. 100) 14Jun2002 (No. 102)
PBO	0433007	Skin Disorder	Excessive Skin due to Obesity and Weight Loss		Once	Res		Severe	NR	Inter	Surgical	Yes	04Apr2002 (No. 092) 10Apr2002 (No. 093)
3 mg ESO	0456007	Uterine Fibroids Enlarged	Uterine Leiomyoma		Once	Res		Moderate	NR	None	Surgical	Yes	09May2002 (No. 099) 24Jun2002 (No. 103) 08Aug2002 (No. 107)
3 mg ESO	0458007	Uterine Fibroids Enlarged	Fibroid Tumors		Once	Res		Moderate	NR	Inter	Surgical	Yes	09May2002 (No. 099) 14Jun2002 (No. 102)

ESO = Esopiclone; PBO = Placebo; Out = outcome; Freq = Frequency; Cont = Continuous; Inter = Intermittent; Res = resolved; Ong = ongoing; Unk = Unknown; Rel = relationship to treatment; NR = not related; Poss = possibly related; Disc = subject discontinued; Intr = study treatment interrupted, UAE = Unexpected Adverse Event

References: CSR 190-049, Appendix 16.2.11.

Table VIII.E.3

Other Serious Adverse Events for Other Non-Integrated Studies (Safety Population)

Treatment	Subject No.	Preferred Term	Reported Term	AE Start Date	Freq	Out	AE End Date	Severity	Rel	Action Taken	AE Treatment	UAE?	IND Safety Report Date and Serial No.
Study 190-013: Subjects with Hepatic Dysfunction													
2 mg ESO	231030	Gastroenteritis	Gastroenteritis		Inter	Res		Severe	NR	None	Medication	Yes	N/A

Eso = Esopiclone; PBO = Placebo; Out = outcome; Freq = Frequency; Cont = Continuous; Inter = Intermittent; Res = resolved; Ong = ongoing; Unk = Unknown; Rel = relationship to treatment; NR = not related, Poss = possibly related; Disc = subject discontinued; Intr = study treatment interrupted; UAE = Unexpected Adverse Event; N/A = Not applicable.

Note: Serious adverse events prior to treatment are not summarized.

Reference: See CSR 190-013, Appendix 16.2.8 for subject 231030.

Table VIII.E.4 A Description of Selected SAEs (taken from the narrative, verbatim, as provided in the submission starting on p. 310 of the ISS.pdf)

Study 190-048, Subject 427004 [Esopiclone 1.0 mg]: Chest pain (not related)
This subject was an 80-year-old Caucasian female with no baseline physical examination results nor findings in her medical history that may be related to the observed SAE. IMDUR was both a prior and concomitant treatment for coronary artery disease. At Baseline (09 July 2001), this subject had abnormal findings (probable sinus bradycardia with occasional atrial premature contractions) that were not considered clinically significant. The subject began dosing with esopiclone 1.0 mg on 17 July 2001. The subject experienced chest pain ("atypical chest pain") at — The subject was treated with nitroglycerine 0.15 mg PRN and the event resolved on — . At Visit 3 (25 July 2001), this subject had abnormal findings (sinus bradycardia and first degree A-V block) that were not considered clinically significant. The event of chest pain was moderate, and the subject completed the study as planned. The event was assessed by the Investigator as serious, not unexpected, and considered it not related to treatment. At Visit 4/End-of-Study (31 July 2001), this subject had abnormal findings (sinus bradycardia, borderline first degree A-V block, and incomplete right bundle branch block) that were not considered clinically significant.

2 SAEs of Uterine Fibroids Enlarged During the 6-month Open-Label ESZ extension phase of Study 190-049:
Subject 0456007 [Open-label Esopiclone 3 mg]: Uterine Fibroids Enlarged
This subject was a 55-year-old Hispanic female with no reported history of reproductive problems or baseline physical examination results that may have been related to the observed adverse event. However, per the IND Safety Report, the subject's relevant medical history included postmenopausal bleeding, pelvic pain, and hypertension. Concomitant medications included Caltrate Plus D, Claritin D, Multivitamins for nutritional supplement, estrogen and progesterone for hormone replacement, Allegra-D for allergies, Zithromax, and Mytussin AC for cough. Her medical history included a tubal ligation in — and menopause in 1996. She was randomly assigned to receive esopiclone 3 mg on 10 April 2001 and was dispensed open-label esopiclone treatment on 08 October 2001. She had a hysterectomy and bilateral salpingo-oophorectomy on — to treat uterine leiomyoma (preferred term: uterine fibroids enlarged), which resolved on — The event was moderate, serious, and the relationship to treatment was not related. The subject was not discontinued for this event and the subject completed the study. The date of last dose of open-label esopiclone was 31 March 2002. (Reference: CSR 190-049; IND Safety Report submitted on 09 May 2002 [Serial No. 099], 24 June 2002 [Serial No. 103], and 08 August 2002 [Serial No. 107].)

Subject 0458007 [Open-label Esopiclone 3 mg]: Uterine Fibroids Enlarged
This subject was a 44-year-old Caucasian female with a history of uterine fibroids (since 1998). She was randomly assigned to receive esopiclone 3 mg on 30 May 2001 and was dispensed open-label esopiclone treatment on 28 November 2001. She had a hysterectomy on — for fibroid tumors (preferred term: uterine fibroids enlarged). Per the investigator's comments, there was no worsening from baseline prior to the SAE. The event was moderate, serious, and the relationship to treatment was not related. The subject was not discontinued for this event; however, study treatment was interrupted. This subject completed the study. The date of last dose of open-label esopiclone was 28 May 2002. (Reference: CSR 190-049; IND Safety Reports submitted on 09 May 2002 [Serial No. 099] and 14 June 2002 [Serial No. 102].)

Table VIII. F. 1. Adverse Dropouts in the Two 2-Week Studies (190-047 and 190-048) of Elderly Chronic Insomnia Patients (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=208) Subject n (%)	Placebo Event n	1 mg [1] (N=100) Subject n (%)	1 mg [1] Event n	2 mg (N=215) Subject n (%)	2 mg Event n
TOTAL (ANY AE)	8 (3.8%)	11	1 (1.0%)	3	5 (2.3%)	7
BODY AS A WHOLE	5 (2.4%)	5	0 (0.0%)	0	1 (0.5%)	1
ASTHENIA	1 (0.5%)	1	0 (0.0%)	0	1 (0.5%)	1
HEADACHE	4 (1.9%)	4	0 (0.0%)	0	0 (0.0%)	0
CARDIOVASCULAR SYSTEM	3 (1.4%)	3	0 (0.0%)	0	0 (0.0%)	0
ARRHYTHMIA	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0
CARDIOVASCULAR DISORDER	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0
MYOCARDIAL INFARCT	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0
DIGESTIVE SYSTEM	0 (0.0%)	0	1 (1.0%)	1	1 (0.5%)	1
DIARRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	1
NAUSEA	0 (0.0%)	0	1 (1.0%)	1	0 (0.0%)	0
NERVOUS SYSTEM	2 (1.0%)	2	1 (1.0%)	2	4 (1.9%)	4
ATAXIA	0 (0.0%)	0	1 (1.0%)	1	0 (0.0%)	0
DIZZINESS	1 (0.5%)	1	0 (0.0%)	0	2 (0.9%)	2
HYPERTONIA	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	1
INSOMNIA	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0
SOMNOLENCE	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	1
VERTIGO	0 (0.0%)	0	1 (1.0%)	1	0 (0.0%)	0
SKIN AND APPENDAGES	1 (0.5%)	1	0 (0.0%)	0	1 (0.5%)	1
PRURITUS	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	1
SWEATING	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0

[1] Subjects from Study 190-047 who received 1.5 mg zaleplon are presented in the 1 mg dose group.
Note: For the cross-over studies, each subject should contribute to only one treatment and/or dose category (applicable to the following studies, 190-012, 190-015, 190-024, 190-025, and 190-045).
Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.
Note: Subject 046-110-061 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 046-149-016 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form.

Reference(s): Listing 4.3.1 and 4.3.2
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Table VIII. F. 2. Adverse Dropouts in the 6-Week Non-Elderly Chronic Insomnia Study 190-046 (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=99)		Eszopiclone 1 mg (N=0)		2 mg (N=104)		2.5 mg (N=0)		3 mg (N=105)		>=3.5 mg (N=0)		All Active (N=209)	
	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
TOTAL (ANY AE)	0 (0.0%)	0	0 (0.0%)	0	2 (1.9%)	4	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (1.0%)	4
BODY AS A WHOLE	0 (0.0%)	0	0 (0.0%)	0	2 (1.9%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (1.0%)	2
HEADACHE	0 (0.0%)	0	0 (0.0%)	0	2 (1.9%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (1.0%)	2
DIGESTIVE SYSTEM	0 (0.0%)	0	0 (0.0%)	0	1 (1.0%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	2
NAUSEA	0 (0.0%)	0	0 (0.0%)	0	1 (1.0%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	1
VOMITING	0 (0.0%)	0	0 (0.0%)	0	1 (1.0%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.5%)	1

Note: For the cross-over studies, each subject should contribute to only one treatment and/or dose category (applicable to the following studies: 190-013, 190-015, 190-024, 190-025, and 190-045).

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

Note: Subject 046-110-061 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 046-143-014 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form.

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Table VIII. F. 3. Adverse Dropouts in the 6-Month Double-Blind Phase of the Non-Elderly Chronic Insomnia Study 190-049 (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=195) Subject n (%)	Placebo (N=195) Event n	Esopiclone 3 mg (N=593) Subject n (%)	Esopiclone 3 mg (N=593) Event n
			76 (12.8%)	146
			18 (3.0%)	31
			2 (0.3%)	2
TOTAL (ANY AE)	14 (7.2%)	24	3 (0.5%)	11
			6 (1.0%)	6
BODY AS A WHOLE	8 (4.1%)	9	3 (0.5%)	3
ABDOMINAL PAIN	0 (0.0%)	0	1 (0.2%)	1
ACCIDENTAL INJURY	0 (0.0%)	0	4 (0.7%)	4
ASTHENIA	3 (1.5%)	3	2 (0.3%)	3
CHEST PAIN	2 (1.0%)	2	1 (0.2%)	1
CYST	0 (0.0%)	0		
HEADACHE	4 (2.1%)	4	5 (0.8%)	5
NEOPLASM	0 (0.0%)	0	1 (0.2%)	1
OVERDOSE	0 (0.0%)	0	2 (0.3%)	2
			2 (0.3%)	2
CARDIOVASCULAR SYSTEM	1 (0.5%)	1		
HEMORRHAGE	0 (0.0%)	0	11 (1.9%)	16
MIGRAINE	0 (0.0%)	0	1 (0.2%)	1
PALPITATION	1 (0.5%)	1		
DIGESTIVE SYSTEM	2 (1.0%)	2		
ANOREXIA	0 (0.0%)	0		

Note: For the cross-over studies, each subject should contribute to only one treatment and/or dose category applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045.

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

Note: Subject 045-210-046 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 048-349-016 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form.

Continued on the next page.

Table VIII. F. 3. Adverse Dropouts in the 6-Month Double-Blind Phase of the Non-Elderly Chronic Insomnia Study 190-049, continued (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=195) Subject n (%)	Placebo (N=195) Event n	Esopiclone 3 mg (N=593) Subject n (%)	Esopiclone 3 mg (N=593) Event n
CONSTIPATION	0 (0.0%)	0	1 (0.2%)	1
DIARRHEA	0 (0.0%)	0	2 (0.3%)	2
DRY MOUTH	2 (1.0%)	2	2 (0.3%)	2
HEPATIC NEOPLASIA	0 (0.0%)	0	1 (0.2%)	1
NAUSEA	0 (0.0%)	0	7 (1.2%)	7
TONGUE EDEMA	0 (0.0%)	0	1 (0.2%)	1
VOMITING	0 (0.0%)	0	1 (0.2%)	1
ENDOCRINE SYSTEM	1 (0.5%)	1	1 (0.2%)	1
HYPOTHYROIDISM	1 (0.5%)	1	1 (0.2%)	1
HEMIC AND LYMPHATIC SYSTEM	0 (0.0%)	0	2 (0.3%)	2
ECCHYMOSIS	0 (0.0%)	0	2 (0.3%)	2
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0%)	0	2 (0.3%)	2
PERIPHERAL EDEMA	0 (0.0%)	0	1 (0.2%)	1
WEIGHT GAIN	0 (0.0%)	0	1 (0.2%)	1

Note: For the cross-over studies, each subject should contribute to only one treatment and/or dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045).

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

Note: Subject 046-316-061 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 048 149-016 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form.

Table VIII. F. 3. Adverse Dropouts in the 6-Month Double-Blind Phase of the Non-Elderly Chronic Insomnia Study 190-049, continued (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=195) Subject n (%)	Placebo (N=195) Event n	Esopiclone 3 mg (N=593) Subject n (%)	Esopiclone 3 mg (N=593) Event n
MUSCULOSKELETAL SYSTEM	0 (0.0%)	0	4 (0.7%)	4
ARTHRALGIA	0 (0.0%)	0	1 (0.2%)	1
ARTHRITIS	0 (0.0%)	0	1 (0.2%)	1
MYALGIA	0 (0.0%)	0	1 (0.2%)	1
TWITCHING	0 (0.0%)	0	1 (0.2%)	1
NERVOUS SYSTEM	6 (3.1%)	8	45 (7.6%)	59
ABNORMAL DREAMS	1 (0.5%)	1	1 (0.2%)	1
AGITATION	0 (0.0%)	0	4 (0.7%)	5
ANXIETY	0 (0.0%)	0	5 (0.8%)	5
APATHY	0 (0.0%)	0	1 (0.2%)	1
DEPRESSION	0 (0.0%)	0	12 (2.0%)	12
DIZZINESS	1 (0.5%)	1	4 (0.7%)	4
EMOTIONAL LABILITY	0 (0.0%)	0	2 (0.3%)	3
HOSTILITY	0 (0.0%)	0	1 (0.2%)	1
HYPERTONIA	0 (0.0%)	0	1 (0.2%)	1
INSOMNIA	3 (1.5%)	3	0 (0.0%)	0
MEMORY IMPAIRMENT	0 (0.0%)	0	2 (0.3%)	2
NERVOUSNESS	0 (0.0%)	0	1 (0.2%)	1

Note: For the cross-over studies, each subject should contribute to only one treatment and/or dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045).

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

Note: Subject 946-119 061 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 048-149-016 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form.

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Table VIII. F. 3. Adverse Dropouts in the 6-Month Double-Blind Phase of the Non-Elderly Chronic Insomnia Study 190-049, continued (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=195) Subject n (%)	Placebo (N=195) Event n	Esopiclone 3 mg (N=593) Subject n (%)	Esopiclone 3 mg (N=593) Event n
NEURALGIA	0 (0.0%)	0	1 (0.2%)	1
NEUROSIS	0 (0.0%)	0	1 (0.2%)	1
PARESTHESIA	0 (0.0%)	0	2 (0.3%)	3
SLEEP DISORDER	0 (0.0%)	0	2 (0.3%)	2
SOMNOLENCE	3 (1.5%)	3	13 (2.2%)	13
THINKING ABNORMAL	0 (0.0%)	0	3 (0.5%)	3
RESPIRATORY SYSTEM	0 (0.0%)	0	1 (0.2%)	1
RHINITIS	0 (0.0%)	0	1 (0.2%)	1
SKIN AND APPENDAGES	1 (0.5%)	1	7 (1.2%)	7
ERYTHEMA MULTIFORME	0 (0.0%)	0	1 (0.2%)	1
HERPES ZOSTER	0 (0.0%)	0	1 (0.2%)	1
PRURITUS	0 (0.0%)	0	1 (0.2%)	1
RASH	1 (0.5%)	1	3 (0.5%)	3
URTICARIA	0 (0.0%)	0	1 (0.2%)	1
SPECIAL SENSES	1 (0.5%)	1	12 (2.0%)	13
ABNORMAL VISION	0 (0.0%)	0	3 (0.5%)	3

Note For the cross-over studies, each subject should contribute to only one treatment and/or dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-049).

Note If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

Note: Subject 044-310-061 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 048 343-016 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form.

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Table VIII. F. 3. Adverse Dropouts in the 6-Month Double-Blind Phase of the Non-Elderly Chronic Insomnia Study 190-049, continued (as provided by the sponsor).

COSTART Body System Preferred Term	Placebo (N=195) Subject n (%)	Placebo (N=195) Event n	Esopiclone 3 mg (N=593) Subject n (%)	Esopiclone 3 mg (N=593) Event n
UNPLEASANT TASTE	1 (0.5%)	1	10 (1.7%)	10
UROGENITAL SYSTEM	1 (0.5%)	1	5 (0.8%)	5
BREAST NEOPLASM	0 (0.0%)	0	1 (0.2%)	1
BREAST PAIN	0 (0.0%)	0	2 (0.3%)	2
METRORRHAGIA	0 (0.0%)	0	1 (0.2%)	1
NOCTURIA	1 (0.5%)	1	0 (0.0%)	0
UTERINE FIBROIDS ENLARGED	0 (0.0%)	0	1 (0.2%)	1

Note: For the cross-over studies, each subject should contribute to only one treatment and/or dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045).

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

Note: Subject 046-310-061 indicated adverse event as reason for early withdrawal on termination form but did not indicate action taken as study drug discontinued on adverse event form. Subject 046-149-016 indicated action taken as study drug discontinued on adverse event form but did not indicate adverse event as reason for early withdrawal on termination form

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Table H. 1.

Adverse Events with an Eszopiclone Incidence of at Least 2% and Greater than the Placebo Incidence by Treatment and Type of Study
(Safety Population)

Study Type = Daytime, 1-7 day studies in Healthy Volunteers [1]

COSTART Body System Preferred Term	Placebo (N=124)		Eszopiclone: 1 mg (N=24)		2 mg (N=42)		2.5 mg (N=6)		3 mg (N=135)		>=3.5 mg (N=91)		All Active (N=295)	
	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
TOTAL (ANY AE)	50 (40.3%)	76	24 (58.3%)	39	42 (80.8%)	124	6 (100%)	11	101 (74.8%)	179	65 (71.4%)	128	228 (77.3%)	441
BODY AS A WHOLE	16 (12.9%)	22	6 (25.0%)	11	6 (11.5%)	6	2 (33.3%)	2	24 (17.8%)	34	15 (16.5%)	26	53 (18.0%)	79
ABDOMINAL PAIN	1 (0.8%)	2	1 (4.2%)	2	0 (0.0%)	0	0 (0.0%)	0	3 (2.2%)	3	2 (2.2%)	2	6 (2.0%)	7
ACCIDENTAL INJURY	2 (0.8%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.7%)	1	3 (3.3%)	4	4 (1.4%)	5
ASTHENIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	10 (7.4%)	12	4 (4.4%)	4	14 (4.7%)	16
CHEST PAIN	1 (0.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
HEADACHE	14 (11.3%)	19	4 (16.7%)	7	5 (9.6%)	5	1 (16.7%)	1	10 (7.4%)	13	9 (9.9%)	14	28 (9.8%)	40
INJECTION SITE HEMORRHAGE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (2.2%)	3	0 (0.0%)	0	3 (1.0%)	3
INJECTION SITE INFLAMMATION	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
INJECTION SITE REACTION	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
PAIN	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1	0 (0.0%)	0	2 (1.5%)	2	2 (2.2%)	2	5 (1.7%)	5
DIGESTIVE SYSTEM	4 (3.2%)	7	2 (8.3%)	2	6 (11.5%)	9	0 (0.0%)	0	20 (14.8%)	27	9 (9.9%)	10	37 (12.5%)	48
ABNORMAL STOOLS	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.1%)	1	2 (0.7%)	2
ANOREXIA	1 (0.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	5 (3.7%)	5	0 (0.0%)	0	5 (1.7%)	5
CONSTIPATION	2 (1.6%)	3	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	4 (3.0%)	4	0 (0.0%)	0	4 (1.4%)	4
DIARRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1	0 (0.0%)	0	3 (2.2%)	3	1 (1.1%)	1	3 (1.4%)	3
DRY MOUTH	1 (0.8%)	2	0 (0.0%)	0	4 (7.7%)	5	0 (0.0%)	0	3 (2.2%)	3	1 (1.1%)	1	8 (2.7%)	9
DYSPEPSIA	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.7%)	1	2 (2.2%)	2	4 (1.4%)	4
FLATULENCE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	6 (4.4%)	6	1 (1.1%)	1	7 (2.4%)	7
NAUSEA	1 (0.8%)	1	0 (0.0%)	0	1 (1.9%)	1	0 (0.0%)	0	4 (3.0%)	5	3 (3.3%)	4	8 (2.7%)	10
HEMIC AND LYMPHATIC SYSTEM	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.7%)	1	1 (1.1%)	1	3 (1.0%)	3
ECCHYMOSIS	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.7%)	1	1 (1.1%)	1	3 (1.0%)	3
MUSCULOSKELETAL SYSTEM	3 (2.4%)	4	1 (4.2%)	1	1 (1.9%)	1	0 (0.0%)	0	3 (2.2%)	6	1 (1.1%)	1	6 (2.0%)	9
MYALGIA	3 (2.4%)	4	1 (4.2%)	1	1 (1.9%)	1	0 (0.0%)	0	3 (2.2%)	6	1 (1.1%)	1	6 (2.0%)	9
NERVOUS SYSTEM	30 (24.2%)	45	9 (37.5%)	21	29 (55.8%)	44	4 (66.7%)	6	83 (61.5%)	239	63 (69.2%)	223	188 (63.7%)	533
ABNORMAL DREAMS	0 (0.0%)	0	1 (4.2%)	1	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.1%)	1	3 (1.0%)	3
ABNORMAL GAIT	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1	0 (0.0%)	0	1 (0.7%)	2	3 (3.3%)	3	5 (1.7%)	6
CONFUSION	1 (0.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	4 (3.0%)	4	3 (3.3%)	5	7 (2.4%)	9
DIZZINESS	14 (11.3%)	15	4 (16.7%)	4	10 (19.2%)	12	1 (16.7%)	1	34 (25.2%)	68	31 (34.1%)	61	80 (27.1%)	146
EMOTIONAL LABILITY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	4 (4.4%)	4	4 (1.4%)	4
INSOMNIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	6 (4.4%)	9	2 (2.2%)	3	8 (2.7%)	12
MEMORY IMPAIRMENT	0 (0.0%)	0	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.1%)	1	2 (0.7%)	2
NERVOUSNESS	1 (0.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (2.2%)	3	1 (1.1%)	1	4 (1.4%)	4
RELAXED FEELING	1 (0.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	4 (3.0%)	4	10 (11.0%)	10	14 (4.7%)	14
SOMNOLENCE	24 (19.4%)	25	8 (33.3%)	14	23 (44.2%)	29	4 (66.7%)	5	71 (52.6%)	146	54 (59.3%)	119	160 (54.2%)	313
SPEECH DISORDER	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1	0 (0.0%)	0	1 (0.7%)	1	3 (3.3%)	10	5 (1.7%)	12
THINKING ABNORMAL	2 (1.6%)	2	1 (4.2%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (1.5%)	2	5 (5.5%)	5	8 (2.7%)	8
RESPIRATORY SYSTEM	5 (4.0%)	6	1 (4.2%)	1	4 (7.7%)	4	0 (0.0%)	0	9 (6.7%)	11	8 (8.8%)	12	22 (7.5%)	28
HICCUP	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	8 (5.9%)	8	4 (4.4%)	7	12 (4.1%)	15
PHARYNGITIS	3 (2.4%)	3	1 (4.2%)	1	1 (1.9%)	1	0 (0.0%)	0	1 (0.7%)	1	3 (3.3%)	3	6 (2.0%)	6
RHINITIS	3 (2.4%)	3	0 (0.0%)	0	3 (5.8%)	3	0 (0.0%)	0	1 (0.7%)	2	2 (2.2%)	2	6 (2.0%)	7
SPECIAL SENSES	12 (9.7%)	12	1 (4.2%)	2	25 (48.1%)	40	3 (50.0%)	3	46 (34.1%)	61	37 (40.7%)	55	112 (38.0%)	161
ABNORMAL VISION	1 (0.8%)	1	0 (0.0%)	0	1 (1.9%)	1	0 (0.0%)	0	2 (1.5%)	2	3 (3.3%)	6	6 (2.0%)	9
DIPLOPIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (2.2%)	2	2 (0.7%)	2
UNPLEASANT TASTE	11 (8.9%)	11	1 (4.2%)	2	24 (46.2%)	39	3 (50.0%)	3	46 (34.1%)	59	35 (38.5%)	47	109 (36.9%)	150

[1] Includes studies 190-001, 190-002, 190-005, 190-010, 190-011, 190-012, 190-013, 190-014, 190-019, 190-020, 190-021, and 190-023.

Note: For the cross over studies, each subject may contribute to more than one treatment and in dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045).

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

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Table H. 2.

All Adverse Events by Treatment and Type of Study
(Safety Population)

Study Type = Nighttime, 1-7 day studies in non-elderly adult healthy volunteers (studies 190-024 and 190-026)

COSTART Body System Preferred Term	Placebo (N=110)		Esopiclone 1 mg (N=47)		Esopiclone 2 mg (N=109)		Esopiclone 2.5 mg (N=0)		Esopiclone 3 mg (N=110)		Esopiclone >=3.5 mg (N=96)		Esopiclone All Active (N=350)	
	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
TOTAL (ANY AE)	23 (20.9%)	29	11 (23.4%)	15	35 (32.1%)	48	0 (0.0%)	0	38 (34.5%)	48	28 (29.2%)	35	109 (31.1%)	146
BODY AS A WHOLE	7 (6.4%)	7	1 (2.1%)	1	6 (5.5%)	7	0 (0.0%)	0	7 (6.4%)	8	5 (5.2%)	6	19 (5.4%)	22
ABDOMINAL PAIN	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	2 (2.1%)	2	3 (0.9%)	3
ACCIDENTAL INJURY	0 (0.0%)	0	0 (0.0%)	0	2 (1.8%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.6%)	2
ASTHENIA	3 (2.7%)	3	0 (0.0%)	0	2 (1.8%)	2	0 (0.0%)	0	1 (0.9%)	1	2 (2.1%)	2	5 (1.4%)	5
FACE EDEMA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	1 (0.3%)	1
HEADACHE	3 (2.7%)	3	1 (2.1%)	1	3 (2.8%)	3	0 (0.0%)	0	5 (4.5%)	5	2 (2.1%)	2	11 (3.1%)	11
INFECTION	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
CARDIOVASCULAR SYSTEM	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
VASODILATATION	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
DIGESTIVE SYSTEM	3 (2.7%)	3	0 (0.0%)	0	2 (1.8%)	2	0 (0.0%)	0	3 (2.7%)	5	0 (0.0%)	0	4 (1.1%)	7
DRY MOUTH	1 (0.9%)	1	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	2 (1.8%)	2	0 (0.0%)	0	2 (0.6%)	3
DYSPEPSIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	1 (0.3%)	1
LIVER FUNCTION TESTS ABNORMAL	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
NAUSEA	1 (0.9%)	1	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	2 (0.6%)	2
VOMITING	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	1 (0.3%)	1
NERVOUS SYSTEM	7 (6.4%)	8	3 (6.4%)	4	7 (6.4%)	8	0 (0.0%)	0	7 (6.4%)	9	8 (8.3%)	8	25 (7.1%)	29
ABNORMAL DREAMS	0 (0.0%)	0	1 (2.1%)	1	1 (0.9%)	1	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	3 (0.9%)	3
ANXIETY	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
DIZZINESS	1 (0.9%)	1	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	4 (4.2%)	4	5 (1.4%)	5
HALLUCINATIONS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPESTHESIA	0 (0.0%)	0	1 (2.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
INSOMNIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.0%)	1	1 (0.3%)	1
NERVOUSNESS	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (1.8%)	2	0 (0.0%)	0	2 (0.6%)	2
NYSTAGMUS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	1 (1.0%)	1	2 (0.6%)	2
SOMNOLENCE	4 (3.6%)	4	2 (4.3%)	2	6 (5.5%)	6	0 (0.0%)	0	4 (3.6%)	4	2 (2.1%)	2	14 (4.0%)	14
THINKING ABNORMAL	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
RESPIRATORY SYSTEM	1 (0.9%)	1	0 (0.0%)	0	4 (3.7%)	4	0 (0.0%)	0	2 (1.8%)	2	1 (1.0%)	1	7 (2.0%)	7
COUGH INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
PHARYNGITIS	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
RHINITIS	0 (0.0%)	0	0 (0.0%)	0	3 (2.8%)	3	0 (0.0%)	0	2 (1.8%)	2	1 (1.0%)	1	6 (1.7%)	6
SKIN AND APPENDAGES	0 (0.0%)	0	2 (4.3%)	2	1 (0.9%)	1	0 (0.0%)	0	1 (0.9%)	1	1 (1.0%)	1	5 (1.4%)	5
HERPES SIMPLEX	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
RASH	0 (0.0%)	0	2 (4.3%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	1 (1.0%)	1	4 (1.1%)	4
SPECIAL SENSES	10 (9.1%)	10	8 (17.0%)	8	24 (22.0%)	25	0 (0.0%)	0	23 (20.9%)	23	19 (19.8%)	19	73 (20.9%)	75
ABNORMAL VISION	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
CONJUNCTIVITIS	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
EAR DISORDER	0 (0.0%)	0	0 (0.0%)	0	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
EAR PAIN	1 (0.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
UNPLEASANT TASTE	8 (7.3%)	8	8 (17.0%)	8	23 (21.1%)	23	0 (0.0%)	0	23 (20.9%)	23	19 (19.8%)	19	72 (20.6%)	73

Note: For the cross-over studies, each subject may contribute to more than one treatment and/or dose category (applicable to the following studies: 190-012, 190-015, 190-024, 190-025, and 190-045).

Note: If a subject has multiple events per Body System or Preferred Term within a treatment or dose category, the subject is counted only once for that row. Percentages are based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category is based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment are not summarized.

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Table H. 3

Adverse Events With an Esopiclone Incidence of ≥2% and Greater Than Placebo for the Nighttime, Short-Term (1-7 Days) Studies in Non-Elderly Adult Subjects With Insomnia (Safety Population)

	Placebo (N=76)		Esopiclone									
			1 mg (N=63)		2 mg (N=75)		2.5 mg (N=65)		3 mg (N=76)		All Active (N=77)	
BODY SYSTEM	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Preferred Term	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Body as a Whole												
Fever	1 (1)	1	0 (0)	0	1 (1)	1	0 (0)	0	1 (1)	1	2 (3)	2
Headache	6 (8)	6	4 (6)	4	4 (5)	5	2 (3)	3	6 (8)	6	12 (16)	18
Pain	1 (1)	1	0 (0)	0	0 (0)	0	1 (2)	1	1 (1)	1	2 (3)	2
Cardiovascular System												
Migraine	0 (0)	0	0 (0)	0	1 (1)	1	0 (0)	0	1 (1)	2	2 (3)	3
Digestive System												
Diarrhea	1 (1)	1	1 (2)	1	0 (0)	0	3 (5)	3	1 (1)	1	5 (6)	5
Dry Mouth	1 (1)	1	0 (0)	0	0 (0)	0	2 (3)	3	2 (3)	2	2 (3)	5
Dyspepsia	1 (1)	1	0 (0)	0	0 (0)	0	2 (3)	2	1 (1)	1	3 (4)	3
Nausea	3 (4)	3	2 (3)	2	1 (1)	1	2 (3)	2	2 (3)	2	7 (9)	7
Vomiting	0 (0)	0	0 (0)	0	1 (1)	1	1 (2)	1	0 (0)	0	2 (3)	2
Musculoskeletal System												
Arthralgia	0 (0)	0	1 (2)	1	0 (0)	0	1 (2)	1	0 (0)	0	2 (3)	2
Myalgia	1 (1)	1	0 (0)	0	2 (3)	2	1 (2)	1	1 (1)	1	4 (5)	4
Nervous System												
Abnormal Dreams	1 (1)	1	1 (2)	1	1 (1)	1	0 (0)	0	1 (1)	1	2 (3)	3
Paresthesia	1 (1)	1	0 (0)	0	0 (0)	0	0 (0)	0	2 (3)	3	2 (3)	3
Somnolence	3 (4)	4	2 (3)	2	2 (3)	2	2 (3)	2	6 (8)	6	10 (13)	12
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Respiratory System												
Pharyngitis	0 (0)	0	0 (0)	0	2 (3)	2	0 (0)	0	2 (3)	2	4 (5)	4
Skin and Appendages												
Rash	0 (0)	0	1 (2)	1	1 (1)	1	0 (0)	0	0 (0)	0	2 (3)	2
Special Senses												
Unpleasant Taste	0 (0)	0	2 (3)	2	5 (7)	6	6 (9)	7	5 (7)	10	9 (12)	25

Note: Studies 190-025 and 190-045 were included.

Note: For these cross-over studies (190-025 and 190-045), each subject contributed to more than one treatment and or dose category.

Note: If a subject had multiple adverse events per Body System or Preferred Term within a treatment or dose category, the subject was counted only once in that row. Percentages were based on the total number of subjects in each treatment or dose category. For sequential cross-over studies, the assignment of adverse events to a treatment or dose category was based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment were not included in the summary.

Reference: I-01 Table 8.2

Table H.4
Adverse Events With an Esopiclone Incidence of ≥2% and Greater Than Placebo for the Nighttime, 2-Week Studies in Elderly Subjects with Insomnia (Safety Population)

	Placebo (N=208)		Esopiclone					
			1 mg (N=100)		2 mg (N=215)		All Active (N=315)	
BODY SYSTEM	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Preferred Term	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Body as a Whole								
Accidental Injury	2 (1)	2	0 (0)	0	6 (3)	9	6 (2)	9
Back Pain	0 (0)	0	2 (2)	3	4 (2)	5	6 (2)	8
Chest Pain	0 (0)	0	2 (2)	2	2 (1)	2	4 (1)	4
Pain	4 (2)	4	4 (4)	4	10 (5)	11	14 (4)	15
Digestive System								
Diarrhea	5 (2)	6	3 (3)	4	5 (2)	5	8 (3)	9
Dry Mouth	4 (2)	4	2 (2)	2	14 (7)	19	16 (5)	21
Dyspepsia	5 (2)	6	5 (5)	6	4 (2)	4	9 (3)	10
Vomiting	1 (1)	1	2 (2)	2	1 (1)	1	3 (1)	3
Nervous System								
Abnormal Dreams	1 (1)	1	4 (4)	4	2 (1)	2	6 (2)	6
Dizziness	5 (2)	7	2 (2)	2	12 (6)	14	14 (4)	16
Nervousness	3 (1)	3	0 (0)	0	5 (2)	6	5 (2)	6
Neuralgia	0 (0)	0	2 (2)	3	0 (0)	0	2 (1)	3
Skin and Appendages								
Pruritis	3 (1)	4	3 (3)	3	3 (1)	4	6 (2)	7
Special Senses								
Unpleasant Taste	1 (1)	1	7 (7)	7	26 (12)	33	33 (10)	40
Urogenital System								
Cystitis	1 (1)	1	3 (3)	3	1 (1)	1	4 (1)	4
Urinary Tract Infection	1 (1)	1	2 (2)	2	0 (0)	0	2 (1)	2

Note: Studies 190-047 and 190-048 were included.
Note: If a subject had multiple adverse events per Body System or Preferred Term within a treatment or dose category, the subject was counted only once in that row. Percentages were based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category was based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment were not summarized.
Reference: EOT Table 8.2

Table H. 5.

Adverse Events With an Esopiclone Incidence of ≥2% and Greater Than Placebo for the Nighttime, 6-Week Study in Non-Elderly Adult Subjects with Insomnia (Safety Population)

	Placebo (N=99)			Esopiclone							
				2 mg (N=104)			3 mg (N=105)			All Active (N=209)	
BODY SYSTEM	Subjects		Events	Subjects		Events	Subjects		Events	Subjects		Events
Preferred Term	n	(%)	N	n	(%)	n	n	(%)	n	n	(%)	n
Body as a Whole												
Headache	13	(13)	30	22	(21)	38	18	(17)	32	40	(19)	70
Infection	3	(3)	3	5	(5)	5	11	(10)	11	16	(8)	16
Viral Infection	1	(1)	1	3	(3)	3	3	(3)	3	6	(3)	6
Digestive System												
Dry Mouth	3	(3)	4	5	(5)	5	7	(7)	8	12	(6)	13
Dyspepsia	4	(4)	7	4	(4)	7	5	(5)	5	9	(4)	12
Nausea	4	(4)	4	5	(5)	5	4	(4)	4	9	(4)	9
Vomiting	1	(1)	1	3	(3)	3	0	(0)	0	3	(1)	3
Nervous System												
Anxiety	0	(0)	0	3	(3)	3	1	(1)	1	4	(2)	4
Confusion	0	(0)	0	0	(0)	0	3	(3)	3	3	(1)	3
Depression	0	(0)	0	4	(4)	4	1	(1)	1	5	(2)	5
Dizziness	4	(4)	4	5	(5)	5	7	(7)	11	12	(6)	16
Hallucinations	0	(0)	0	1	(1)	3	3	(3)	3	4	(2)	6
Libido Decreased	0	(0)	0	0	(0)	0	3	(3)	3	3	(1)	3
Nervousness	3	(3)	4	5	(5)	6	0	(0)	0	5	(2)	6
Somnolence	3	(3)	4	10	(10)	10	8	(8)	10	18	(9)	20
Skin and Appendages												
Rash	1	(1)	1	3	(3)	3	4	(4)	4	7	(3)	7
Special Senses												
Unpleasant Taste	3	(3)	4	18	(17)	27	36	(34)	43	54	(26)	70

Note: Study 190-046 was included.

Note: If a subject had multiple adverse events per Body System or Preferred Term within a treatment or dose category, the subject was counted only once in that row. Percentages were based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category was based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment were not summarized.

Reference: EOT Table 8.2

Table H. 6

Adverse Events With an Esopiclone Incidence of ≥2% and Greater Than Placebo for the Nighttime, 6-Month Double-blind Study in Non-Elderly Adult Subjects with Insomnia (Safety Population)

	Placebo (N=195)			Esopiclone 3 mg (N=593)		
BODY SYSTEM	Subjects		Events	Subjects		Events
Preferred Term	n	(%)	n	n	(%)	n
Body as a Whole						
Abdominal Pain	11	(6)	17	48	(8)	61
Accidental Injury	11	(6)	13	43	(7)	55
Back Pain	6	(3)	10	45	(8)	68
Chest Pain	6	(3)	6	23	(4)	28
Fever	1	(1)	1	12	(2)	14
Headache	37	(19)	76	116	(20)	235
Infection	13	(7)	14	94	(16)	112
Neck Pain	1	(1)	1	12	(2)	13
Pain	12	(6)	18	67	(11)	94
Digestive System						
Constipation	3	(2)	3	15	(3)	21
Diarrhea	14	(7)	26	45	(8)	61
Dry Mouth	3	(2)	3	39	(7)	43
Nausea	11	(6)	12	67	(11)	93
Metabolic and Nutritional Disorders						
Peripheral Edema	2	(1)	2	14	(2)	16
Musculoskeletal System						
Arthralgia	2	(1)	2	19	(3)	20
Nervous System						
Anxiety	4	(2)	4	22	(4)	26

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Table H. 6, continued.

	Placebo (N=195)			Esopiclone 3 mg (N=593)		
BODY SYSTEM	Subjects		Events	Subjects		Events
Preferred Term	n	(%)	n	n	(%)	n
Depression	3	(2)	4	27	(5)	28
Dizziness	6	(3)	7	58	(10)	76
Nervousness	4	(2)	4	20	(3)	25
Somnolence	5	(3)	5	54	(9)	68
Respiratory System						
Cough Increased	4	(2)	5	15	(3)	16
Pharyngitis	10	(5)	12	59	(10)	71
Rhinitis	9	(5)	9	42	(7)	56
Skin and Appendages						
Rash	6	(3)	6	31	(5)	37
Special Senses						
Otitis Media	1	(1)	1	12	(2)	15
Unpleasant Taste	11	(6)	11	155	(26)	216
Urogenital System						
Dysmenorrhea	4	(2)	5	16	(3)	18
Urinary Tract Infection	2	(1)	3	13	(2)	15

Note: Study 190-049 was included.
Note: If a subject had multiple adverse events per Body System or Preferred Term within a treatment or dose category, the subject was counted only once in that row. Percentages were based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category was based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment were not summarized.
Reference: EOT Table 8.2.

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Table H 7 Study 190-049

Treatment-emergent Adverse Events with an Incidence of ≥2% that Occurred During the Open-label Period (Safety Population)

(This Table also Shows How Subjects within each category of Open-Label Phase AEs were Distributed among Treatment Groups During the Previous 6-Month Double-Blind Phase).

	Open-Label Esopiclone 3 mg (n=471)		Previous Double-blind Treatment			
			Placebo (n=111)		Esopiclone 3 mg (n=360)	
Body System Preferred Term	Subjects [1] n (%)	Events [2] n	Subjects [1] n (%)	Events [2] n	Subjects [1] n (%)	Events [2] n
Body as a Whole						
Abdominal Pain	14 (3.0)	19	4 (3.6)	4	10 (2.8)	15
Accidental Injury	33 (7.0)	37	8 (7.2)	10	25 (6.9)	27
Back Pain	24 (5.1)	35	3 (2.7)	4	21 (5.8)	31
Chest Pain	16 (3.4)	17	6 (5.4)	6	10 (2.8)	11
Flu Syndrome	33 (7.0)	39	4 (3.6)	4	29 (8.1)	35
Headache	51 (10.8)	94	16 (14.4)	27	35 (9.7)	67
Infection	108 (22.9)	137	26 (23.4)	31	82 (22.8)	106
Injection Site Pain	11 (2.3)	13	5 (4.5)	6	6 (1.7)	7
Pain	36 (7.6)	49	7 (6.3)	7	29 (8.1)	42
Viral Infection	18 (3.8)	20	1 (0.9)	1	17 (4.7)	19
Digestive System						
Diarrhea	22 (4.7)	27	3 (2.7)	3	19 (5.3)	24
Dry Mouth	10 (2.1)	10	2 (1.8)	2	8 (2.2)	8
Dyspepsia	22 (4.7)	31	5 (4.5)	11	17 (4.7)	20
Nausea	19 (4.0)	20	3 (2.7)	3	16 (4.4)	17

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Table H 8. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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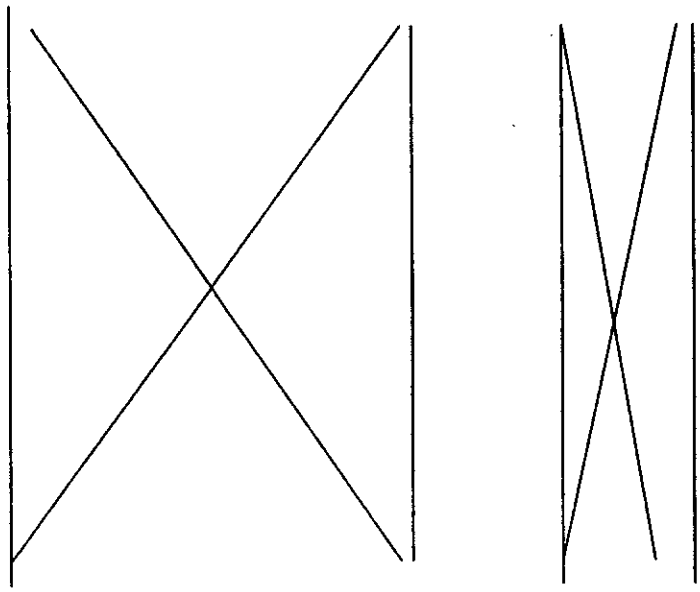

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Table H 8. Continued. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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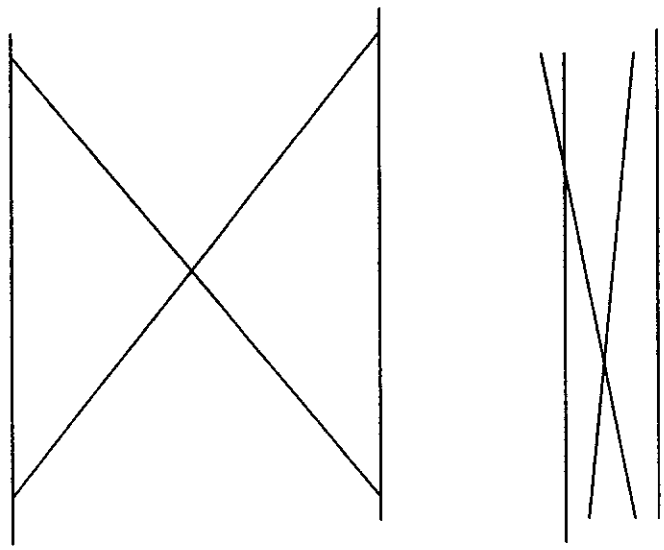

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Table H 8. Continued. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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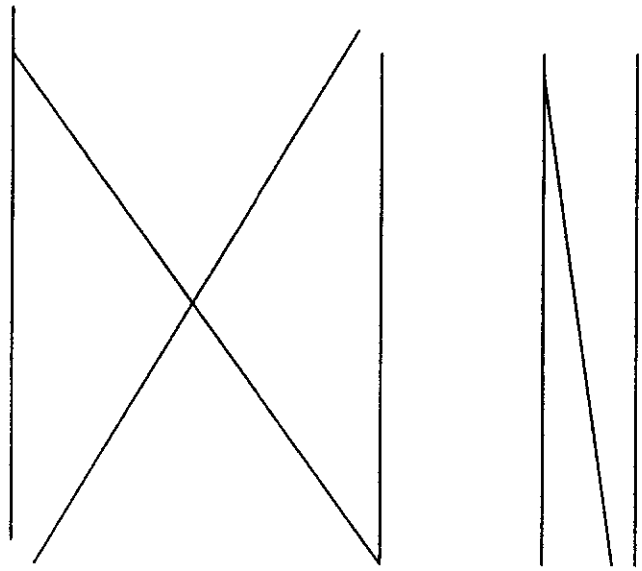

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Table H 8. Continued. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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Table H 8. Continued. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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Table H 8. Continued Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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Table H. 8. Continued. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

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Table H8. Continued. Double-Blind Phase of Study 190-049 (crossed out columns are treatment groups that did not exist in this study).

Table 6.1

All Adverse Events by Treatment and Type of Study
(Safety Population)

Study Type = Nighttime, long-term (6 month double-blind) study in non-elderly adult subjects with insomnia (study 190-049)

COSTART Body System Preferred Term	Placebo (N=195)		Esopiclone 1 mg (N=0)		Esopiclone 2 mg (N=0)		Esopiclone 2.5 mg (N=0)		Esopiclone 3 mg (N=593)		Esopiclone >=3.5 mg (N=0)		Esopiclone All Active (N=593)	
	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n
MENORRHAGIA	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.5%)	3	0 (0.0%)	0	3 (0.5%)	3
METRORRHAGIA	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.3%)	2	0 (0.0%)	0	2 (0.3%)	2
NOCTURIA	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
OLIGURIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.2%)	1	0 (0.0%)	0	1 (0.2%)	1
PROSTATE NEOPLASIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.2%)	1	0 (0.0%)	0	1 (0.2%)	1
PYELONEPHRITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.2%)	1	0 (0.0%)	0	1 (0.2%)	1
URETHRITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.2%)	1	0 (0.0%)	0	1 (0.2%)	1
URINARY FREQUENCY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.5%)	3	0 (0.0%)	0	3 (0.5%)	3
URINARY INCONTINENCE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.3%)	2	0 (0.0%)	0	2 (0.3%)	2
URINARY TRACT DISORDER	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
URINARY TRACT INFECTION	2 (1.0%)	3	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	13 (2.2%)	15	0 (0.0%)	0	13 (2.2%)	15
URINE ABNORMALITY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.3%)	2	0 (0.0%)	0	2 (0.3%)	2
UTERINE FIBROIDS ENLARGED	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.3%)	3	0 (0.0%)	0	2 (0.3%)	3
UTERINE HEMORRHAGE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.2%)	1	0 (0.0%)	0	1 (0.2%)	1
VAGINAL HEMORRHAGE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.5%)	3	0 (0.0%)	0	3 (0.5%)	3
VAGINAL MONILIASIS	1 (0.5%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	9 (1.5%)	12	0 (0.0%)	0	9 (1.5%)	12
VAGINITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	4 (0.7%)	4	0 (0.0%)	0	4 (0.7%)	4
VULVOVAGINAL DISORDER	1 (0.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0

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Table H9. Open Label Phase (This Table also Shows How Subjects within each category of Open-Label Phase AEs were Distributed among Treatment Groups During the Previous 6-Month Double-Blind Phase).

Treatment Emergent Adverse Events
(Safety Population)

Treatment Period: Open-Label

	Open-Label Eszopiclone 3 mg [1] (N=471)		Double-Blind Treatment: Placebo (N=111)		Double-Blind Treatment: Eszopiclone 3 mg (N=362)	
Body System / Preferred Term	Subjects [2] n (%)	Events [3] n	Subjects [2] n (%)	Events [3] n	Subjects [2] n (%)	Events [3] n
Overall	354 (75.2%)	1822	85 (76.6%)	298	269 (74.3%)	1524
BODY AS A WHOLE	239 (50.7%)	516	55 (49.5%)	110	184 (51.1%)	406
ABDOMINAL PAIN	14 (3.0%)	15	4 (3.6%)	4	10 (2.8%)	15
ABSCESS	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
ACCIDENTAL INJURY	33 (7.0%)	37	8 (7.2%)	10	25 (6.9%)	27
ALLERGIC REACTION	6 (1.3%)	7	0 (0.0%)	0	6 (1.7%)	7
ASTHENIA	6 (1.3%)	8	0 (0.0%)	0	6 (1.7%)	8
BACK PAIN	24 (5.1%)	35	3 (2.7%)	4	21 (5.8%)	31
CELLULITIS	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
CHEST PAIN	16 (3.4%)	17	6 (5.4%)	6	10 (2.8%)	11
CYST	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
FACE EDEMA	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
FEVER	8 (1.7%)	8	2 (1.8%)	2	6 (1.7%)	6
FLU SYNDROME	33 (7.0%)	35	4 (3.6%)	4	29 (8.1%)	35
HEADACHE	51 (10.8%)	94	16 (14.4%)	27	35 (9.7%)	67
HERNIA	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
INFECTION	108 (22.9%)	137	26 (23.4%)	31	82 (22.8%)	106
INFECTION BACTERIAL	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
INFECTION FUNGAL	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
INFECTION PARASITIC	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
INJECTION SITE EDEMA	2 (0.4%)	2	2 (1.8%)	2	0 (0.0%)	0
INJECTION SITE PAIN	11 (2.3%)	13	5 (4.5%)	6	6 (1.7%)	7
INSECT BITE	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
NECK PAIN	8 (1.7%)	9	2 (0.0%)	0	6 (2.2%)	9
NECK RIGIDITY	4 (0.8%	4	1 (0.9%)	1	3 (0.8%	3
PAIN	36 (7.6%)	46	7 (6.3%	7	29 (8.1%)	42
PELVIC PAIN	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
VIRAL INFECTION	18 (3.8%)	20	1 (0.9%)	1	17 (4.7%)	19
CARDIOVASCULAR SYSTEM	29 (6.2%)	30	10 (9.0%)	10	19 (5.3%)	20
AORTIC STENOSIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
ARRHYTHMIA	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
ATRIAL FIBRILLATION	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
BRADYCARDIA	1 (0.2%	1	0 (0.0%)	0	1 (0.3%)	1
BUNDLE BRANCH BLOCK	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
CARDIOVASCULAR DISORDER	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
HYPERTENSION	7 (1.5%)	7	2 (1.8%)	2	5 (1.4%)	5
MIGRAINE	2 (0.4%)	3	0 (0.0%)	0	2 (0.6%)	3
PALPITATION	6 (1.3%)	6	5 (4.5%)	5	1 (0.3%)	1
PERICARDIAL EFFUSION	1 (0.2%)	1	0 (0.0%	0	1 (0.3%)	1
PERIPHERAL VASCULAR DISORDER	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
PR INTERVAL PROLONGED	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
TACHYCARDIA	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
VARICOSE VEIN	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
VENTRICULAR EXTRASYSTOLES	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
DIGESTIVE SYSTEM	88 (18.7%)	144	19 (17.1%)	27	69 (19.2%)	117

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Table H9. Open Label Phase (This Table also Shows How Subjects within each category of Open-Label Phase AEs were Distributed among Treatment Groups During the Previous 6-Month Double-Blind Phase).

Treatment Emergent Adverse Events
(Safety Population)

Treatment Period: Open-Label

Body System / Preferred Term	Open-Label Eszopiclone 3 mg [1] (N=471) Subjects [2] n (%)	Open-Label Eszopiclone 3 mg [1] (N=471) Events [3] n	Double-Blind Treatment: Placebo (N=111) Subjects [2] n (%)	Placebo (N=111) Events [3] n	Double-Blind Treatment: Eszopiclone 3 mg (N=360) Subjects [2] n (%)	Eszopiclone 3 mg (N=360) Events [3] n
ANOREXIA	2 (0.4%)	2	2 (1.8%)	2	0 (0.0%)	0
CARDIOSPASM	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
CHOLELITHIASIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
COLITIS	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
CONSTIPATION	9 (1.9%)	10	1 (0.9%)	1	8 (2.2%)	9
DIARRHEA	22 (4.7%)	27	3 (2.7%)	3	19 (5.3%)	24
DRY MOUTH	10 (2.1%)	10	2 (1.8%)	2	8 (2.2%)	8
DYSPEPSIA	22 (4.7%)	31	5 (4.5%)	11	17 (4.7%)	20
FLATULENCE	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
GASTRITIS	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
GASTROENTERITIS	4 (0.8%)	4	0 (0.0%)	0	4 (1.1%)	4
GASTROINTESTINAL DISORDER	4 (0.8%)	5	0 (0.0%)	0	4 (1.1%)	5
GINGIVITIS	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
GUM HEMORRHAGE	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
HEPATOMEGALY	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
INCREASED SALIVATION	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
MOUTH ULCERATION	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
NAUSEA	19 (4.0%)	20	3 (2.7%)	3	16 (4.4%)	17
PERIODONTAL ABSCESS	3 (0.6%)	4	0 (0.0%)	0	3 (0.8%)	4
SALIVARY GLAND ENLARGEMENT	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
STOMATITIS	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
TOOTH CARIES	4 (0.8%)	6	0 (0.0%)	0	4 (1.1%)	6
VOMITING	7 (1.5%)	7	1 (0.9%	1	6 (1.7%)	6
ENDOCRINE SYSTEM	7 (1.5%)	7	3 (2.7%)	3	4 (1.1%	4
DIABETES MELLITUS	3 (0.6%)	3	1 (0.9%)	1	2 (0.6%	2
HYPERTHYROIDISM	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
HYPOTHYROIDISM	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
THYROID DISORDER	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
HEMIC AND LYMPHATIC SYSTEM	9 (1.9%)	10	3 (2.7%)	3	6 (1.7%)	7
ANEMIA	2 (0.4%)	2	2 (1.8%)	2	0 (0.0%)	0
ECCHYMOSIS	4 (0.8%)	5	0 (0.0%)	0	4 (1.1%	5
LYMPHADENOPATHY	3 (0.6%)	3	1 (0.9%)	1	2 (0.6%)	2
METABOLIC AND NUTRITIONAL DISORDERS	12 (2.5%)	19	5 (4.5%)	7	7 (1.9%)	12
EDEMA	2 (0.4%)	2	1 (0.9%	1	1 (0.3%)	1
GOUT	3 (0.6%)	3	1 (0.9%	1	2 (0.6%)	2
HYPERCALCEMIA	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPERCHOLESTEREMIA	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPOKALEMIA	4 (0.8%)	4	0 (0.0%)	0	4 (0.8%)	4
HYPOMAGNESEMIA	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
PERIPHERAL EDEMA	5 (1.1%)	7	3 (2.7%)	5	2 (0.6%)	2
WEIGHT LOSS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
MUSCULOSKELETAL SYSTEM	36 (7.6%)	53	9 (8.1%)	10	27 (7.5%)	43
ARTHRALGIA	5 (1.1%)	7	2 (1.8%)	2	3 (0.8%)	5
ARTHRITIS	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%	2

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Table H9, continued. Open Label Phase (This Table also Shows How Subjects within each category of Open-Label Phase AEs were Distributed among Treatment Groups During the Previous 6-Month Double-Blind Phase).

Treatment Emergent Adverse Events
(Safety Population)

Treatment Period: Open-Label

Body System / Preferred Term	Open-Label Eszopiclone 3 mg [1] (N=471) Subjects [2] n (%)	Open-Label Eszopiclone 3 mg [1] (N=471) Events [3] n	Double-Blind Treatment: Placebo (N=111) Subjects [2] n (%)	Placebo (N=111) Events [3] n	Eszopiclone 3 mg (N=360) Subjects [2] n (%)	Eszopiclone 3 mg (N=360) Events [3] n
JOINT DISORDER	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
LEG CRAMPS	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
MYALGIA	21 (4.5%)	24	5 (4.5%)	6	16 (4.4%)	28
MYASTHENIA	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
OSTEOPOROSIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
TENDON DISORDER	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
TWITCHING	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
NERVOUS SYSTEM	76 (16.1%)	115	24 (21.6%)	33	52 (14.4%)	82
ABNORMAL DREAMS	14 (3.0%)	17	4 (3.6%)	4	10 (2.8%)	13
AGITATION	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
ANXIETY	7 (1.5%)	10	4 (3.6%)	5	5 (1.4%)	5
CONFUSION	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
DEPRESSION	7 (1.5%)	8	2 (1.8%)	2	5 (1.4%)	6
DIZZINESS	16 (3.4%)	18	6 (5.4%)	6	10 (2.8%)	12
EMOTIONAL LABILITY	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
HALLUCINATIONS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPERTONIA	7 (1.5%)	9	0 (0.0%)	0	7 (1.9%)	9
INSOMNIA	7 (1.5%)	7	2 (1.8%)	2	5 (1.4%)	5
LIBIDO DECREASED	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
MEMORY IMPAIRMENT	4 (0.8%)	4	1 (0.9%)	1	3 (0.8%)	3
NERVOUSNESS	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
NEURALGIA	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
NEURITIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
NEUROSIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
REFLEXES DECREASED	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
SOMNOLENCE	19 (4.0%)	19	5 (4.5%)	6	10 (2.8%)	10
THINKING ABNORMAL	4 (0.8%)	4	1 (0.9%)	1	3 (0.8%)	3
TREMOR	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
VASODILATATION	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
VERTIGO	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
RESPIRATORY SYSTEM	127 (26.7%)	175	17 (15.3%)	24	90 (25.0%)	142
ASTHMA	4 (0.8%)	5	1 (0.9%)	2	3 (0.8%)	3
BRONCHITIS	8 (1.7%)	8	2 (1.8%)	2	6 (1.7%)	6
COUGH INCREASED	12 (2.5%)	16	2 (1.8%)	2	10 (2.8%)	14
DYSPNEA	7 (1.5%)	7	1 (0.9%)	1	6 (1.7%)	6
EPISTAXIS	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
HEMOPTYSIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
LARYNGITIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
LUNG DISORDER	5 (1.1%)	5	1 (0.9%)	1	4 (1.1%)	4
PHARYNGITIS	27 (5.7%)	39	3 (2.7%)	4	24 (6.7%)	35
PNEUMONIA	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
RHINITIS	31 (6.6%)	38	4 (3.6%)	6	25 (6.9%)	29
SINUSITIS	37 (7.9%)	47	8 (7.2%)	12	29 (8.1%)	35
STRIDOR	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
VOICE ALTERATION	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1

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Table H9, continued. Open Label Phase (This Table also Shows How Subjects within each category of Open-Label Phase AEs were Distributed among Treatment Groups During the Previous 6-Month Double-Blind Phase).

Treatment Emergent Adverse Events
(Safety Population)

Treatment Period: Open-Label

			Double-Blind Treatment			
	Open-Label Eszopiclone 1 mg [1] (N=471)		Placebo (N=111)		Eszopiclone 1 mg (N=360)	
Body System / Preferred Term	Subjects [2] n (%)	Events [3] n	Subjects [2] n (%)	Events [3] n	Subjects [2] n (%)	Events [3] n
SKIN AND APPENDAGES	16 (8.5%)	47	10 (9.0%)	12	30 (8.3%)	35
ACNE	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
ALOPECIA	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
CONTACT DERMATITIS	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
DRY SKIN	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
FUNGAL DERMATITIS	3 (0.6%)	4	0 (0.0%)	0	3 (0.8%)	4
HERPES SIMPLEX	2 (0.4%)	3	1 (0.9%)	1	1 (0.3%)	2
ICHTHYOSIS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
MACULOPAPULAR RASH	3 (0.6%)	3	1 (0.9%)	1	2 (0.6%)	2
PRURITUS	5 (1.1%)	5	1 (0.9%)	1	2 (0.6%)	2
RASH	10 (2.1%)	10	3 (2.7%)	3	7 (1.9%)	7
SEBORRHEA	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
SKIN BENIGN NEOPLASM	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
SKIN DISORDER	4 (0.8%)	5	1 (0.9%)	1	3 (0.8%)	4
SKIN HYPERTROPHY	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
SWEATING	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
URTICARIA	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
VESICULOBULLOUS RASH	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
SPECIAL SENSES	57 (12.1%)	99	27 (24.3%)	31	33 (9.2%)	68
ABNORMAL VISION	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
CONJUNCTIVITIS	6 (1.3%)	6	1 (0.9%)	1	5 (1.4%)	5
EAR DISORDER	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
EAR PAIN	8 (1.7%)	10	1 (0.9%)	2	7 (1.9%)	8
EYE HEMORRHAGE	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
GLAUCOMA	1 (0.2%)	2	0 (0.0%)	0	1 (0.3%)	2
IRITIS	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
LACRIMATION DISORDER	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
OTITIS MEDIA	7 (1.5%)	7	3 (2.7%)	3	4 (1.1%)	4
UNPLEASANT TASTE	32 (6.8%)	56	22 (19.8%)	23	10 (2.8%)	43
VESTIBULAR DISORDER	1 (0.2%)	1	1 (0.9%)	0	1 (0.3%)	1
VITREOUS DISORDER	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
UROGENITAL SYSTEM	67 (14.2%)	107	16 (14.4%)	18	55 (15.3%)	89
AMENORRHEA	1 (0.2%)	1	1 (0.9%)	0	1 (0.3%)	1
BLADDER NEOPLASM	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
BREAST NEOPLASM	1 (0.2%)	1	1 (0.9%)	1	0 (0.0%)	0
BREAST PAIN	7 (1.1%)	7	0 (0.0%)	0	5 (1.4%)	7
CERVIX NEOPLASM	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
CYSTITIS	2 (0.4%)	2	2 (1.8%)	2	0 (0.0%)	0
DYSMENORRHEA	7 (1.5%)	18	1 (0.9%)	2	6 (1.7%)	16
DYSURIA	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
FIBROCYSTIC BREAST	5 (1.1%)	5	0 (0.0%)	0	5 (1.4%)	5
HEMATURIA	7 (1.7%)	8	0 (0.0%)	0	8 (2.2%)	8
HYPOMENORRHEA	1 (0.2%)	1	1 (0.9%)	1	2 (0.6%)	2
KIDNEY CALCULUS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
KIDNEY PAIN	1 (0.2%)	1	2 (1.8%)	0	1 (0.3%)	1
METRORRHAGIA	5 (1.1%)	5	0 (0.0%)	0	5 (1.4%)	5

(1) All subjects received eszopiclone 1 mg during the open-label treatment period.
(2) Subjects are counted only once within each body system and each preferred term.
(3) Event = the total number of events occurring where a single subject may experience multiple events.
Note(s): Open-label emergent adverse events are those events that occurred after administration of open-label study medication.

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Table H9, continued. Open Label Phase (This Table also Shows How Subjects within each category of Open-Label Phase AEs were Distributed among Treatment Groups During the Previous 6-Month Double-Blind Phase).

Treatment Emergent Adverse Events
(Safety Population)

Treatment Period: Open-Label

			Double-Blind Treatment			
	Open-Label Eszopiclone 3 mg [1] (N=471)		Placebo (N=111)		Eszopiclone 3 mg (N=360)	
Body System Preferred Term	Subjects [2] n (%)	Events [3] n	Subjects [2] n (%)	Events [3] n	Subjects [2] n (%)	Events [3] n
PAPANICOLAU SMEAR SUSPICIOUS	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
URINARY FREQUENCY	2 (0.4%)	2	1 (0.9%)	1	1 (0.3%)	1
URINARY TRACT DISORDER	2 (0.4%)	2	0 (0.0%)	0	2 (0.6%)	2
URINARY TRACT INFECTION	21 (4.5%)	26	7 (6.3%)	8	14 (4.9%)	17
URINE ABNORMALITY	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
UTERINE FIBROIDS ENLARGED	3 (0.6%)	3	0 (0.0%)	0	3 (0.8%)	3
UTERINE HEMORRHAGE	1 (0.2%)	1	0 (0.0%)	0	1 (0.3%)	1
VAGINAL MONILIASIS	11 (2.3%)	11	3 (2.7%)	3	8 (2.2%)	8
VAGINITIS	4 (0.9%)	5	0 (0.0%)	0	4 (1.1%)	5

[1] All subjects received eszopiclone 3 mg during the open-label treatment period.
[2] Subjects are counted only once within each body system and each preferred term.
[3] Event = the total number of events occurring where a single subject may experience multiple events.
Note(s): Open-label emergent adverse events are those events that occurred after administration of open-label study medication.

Reference(s): Listing 16.2.10
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Table H 10.

Adverse Events With an Esopiclone Incidence of ≥2% and Greater Than Placebo for a Nighttime, 2-Week Study in Elderly Subjects with Insomnia (Study 190-048) (Safety Population)

	Placebo (N=80)		Esopiclone 1 mg (N=72)		Esopiclone 2 mg (N=79)	
BODY SYSTEM	Subjects	Events	Subjects	Events	Subjects	Events
Preferred Term	n (%)	n	n (%)	n	n (%)	n
Body as a Whole						
Accidental Injury	0 (0)	0	0 (0)	0	2 (3)	4
Asthenia	2 (3)	2	2 (3)	3	2 (3)	5
Headache	12 (15)	17	11 (15)	19	12 (15)	22
Pain	0 (0)	0	3 (4)	3	2 (3)	2
Photosensitivity Reaction	0 (0)	0	0 (0)	0	2 (3)	2
Digestive System						
Diarrhea	0 (0)	0	3 (4)	4	1 (1)	1
Dry Mouth	2 (3)	2	2 (3)	2	2 (3)	2
Dyspepsia	3 (4)	3	4 (6)	5	1 (1)	1
Flatulence	1 (1)	1	0 (0)	0	2 (3)	3
Nausea	2 (3)	2	3 (4)	3	0 (0)	0
Nervous System						
Abnormal Dreams	0 (0)	0	2 (3)	2	1 (1)	1
Confusion	0 (0)	0	0 (0)	0	2 (3)	4
Neuralgia	0 (0)	0	2 (3)	3	0 (0)	0
Respiratory System						
Dyspnea	1 (1)	1	0 (0)	0	2 (3)	2
Skin and Appendages						
Pruritis	0 (0)	0	3 (4)	3	1 (1)	2
Special Senses						
Unpleasant Taste	1 (1)	1	6 (8)	6	9 (11)	11
Urogenital System						
Urinary Incontinence	0 (0)	0	0 (0)	0	2 (3)	2
Urinary Tract Infection	1 (1)	1	2 (3)	2	0 (0)	0

Note: Study 190-048 was included.

Note: If a subject had multiple adverse events per Body System or Preferred Term within a treatment or dose category, the subject was counted only once in that row. Percentages were based on the total number of subjects in each treatment or dose category. For sequential/cross-over studies, the assignment of adverse events to a treatment or dose category was based on the time period beginning on the start day of that treatment or dose to the day prior to the start date of the next treatment or dose. Adverse events prior to treatment or more than 14 days after treatment were not summarized.

Table VIIIL.H.11. Panels A-B Subgroup analyses results of 2 and 6-week Non-Elderly Studies 190-046, -047 and Elderly Study 190-048 (data is combined, noting that age-group comparisons are in essence between the results of these two combined non-elderly trials to the results of the elderly trial).

Panel A.

Treatment-emergent Adverse Events with a Difference in the Treatment Effect of >5% for Age Group

Body System Preferred Term	Placebo n (%)		Esopiclone ≥2 mg n (%)	
	18-64 years (N=104)	≥65 years (N=203)	18-64 years (N=215)	≥65 years (N=209)
Body as a Whole				
Infection	3 (3)	9 (4)	16 (7)	4 (2)
Pain	9 (9)	4 (2)	10 (5)	10 (5)
Special Senses				
Unpleasant Taste	3 (3)	1 (1)	56 (26)	24 (11)

Reference: EOT Table 9.7

Panel B.

Treatment-emergent Adverse Events with a Difference in the Treatment Effect of >5% for Race

Body System Preferred Term	Placebo n (%)			Esopiclone ≥2 mg n (%)		
	Caucasian (N=254)	Black (N=29)	Hispanic (N=18)	Caucasian (N=340)	Black (N=44)	Hispanic (N=31)
Body as a Whole						
Accidental Injury	5 (2)	0 (0)	2 (11)	13 (4)	1 (2)	0 (0)
Back Pain	5 (2)	0 (0)	1 (6)	10 (3)	1 (2)	0 (0)
Headache	38 (15)	1 (3)	2 (11)	59 (17)	6 (14)	3 (10)
Digestive System						
Dyspepsia	6 (2)	1 (3)	2 (11)	7 (2)	0 (0)	5 (16)
Nervous System						
Somnolence	17 (7)	0 (0)	0 (0)	21 (6)	4 (9)	3 (10)
Special Senses						
Unpleasant Taste	2 (1)	0 (0)	2 (11)	58 (17)	5 (11)	11 (35)

Reference: EOT Table 9.8

Table VIIII.H12. Panels A-B Subgroup analyses results of 6-month Double-blind Phase of Study 190-049

Panel A.

Treatment-emergent Adverse Events with a Difference in the Treatment Effect of >5% for Race

Body System Preferred Term	Placebo n (%)		Esopiclone 3 mg n (%)	
	Caucasian (N=153)	Black (N=27)	Caucasian (N=469)	Black (N=77)
Body as a Whole				
Accidental Injury	7 (5)	3 (11)	36 (8)	2 (3)
Back Pain	6 (4)	0 (0)	34 (7)	7 (9)
Chest Pain	6 (4)	0 (0)	14 (3)	4 (5)
Pain	10 (7)	1 (4)	52 (11)	13 (17)
Digestive System				
Diarrhea	7 (5)	5 (19)	34 (7)	6 (8)
Nausea	7 (5)	3 (11)	54 (12)	8 (10)
Nervous System				
Depression	2 (1)	1 (4)	23 (5)	1 (1)
Somnolence	3 (2)	1 (4)	45 (10)	5 (6)

Reference: EOT Table 9.11

Panel B.

Treatment-emergent Adverse Events with a Difference in the Treatment Effect of >5% for Gender

Body System Preferred Term	Placebo n (%)		Esopiclone 3 mg n (%)	
	Male (N=70)	Female (N=125)	Male (N=220)	Female (N=373)
Body as a Whole				
Headache	12 (17)	25 (20)	31 (14)	85 (23)
Digestive System				
Dyspepsia	7 (10)	6 (5)	10 (5)	31 (8)
Nervous System				
Depression	2 (3)	1 (1)	5 (2)	22 (6)
Respiratory System				
Pharyngitis	6 (9)	4 (3)	15 (7)	44 (12)

Reference: EOT Table 9.12

Table VIII.J.1. Clinical Laboratory In-Text Tables (time-points of data used for ISS Summary Tables).

In Text Table Numbers	Studies Included in Analysis	Analysis Assessment Timepoint per Study
Daytime, short-term (1-7 days) studies in healthy volunteers		
8./10.H.12.1.1.1-1 (summ) **8./10.H.12.1.1.2-1** (shift)	190-001 (n=108)	2 days post dose
	190-002 (n=48)	2 days post dose
	190-005 (n=36)	2 days post dose
	190-010 (n=18)	1-2 days post dose
	190-011 (n=79)	1 day post dose
	190-012 (n=14)	Up to 7 days post dose
	190-015 (n=24)	1 day post dose
	190-018 (n=40)	3 days post dose
	190-019 (n=36)	1 day post dose
	190-020 (n=40)	1 day post dose
	190-021 (n=12)	6-20 days post dose
	190-023 (n=18)	2 days post dose
Nighttime, short-term (1-7 days) studies in non-elderly adult healthy volunteers		
8./10.H.12.1.2.1-1 (summ) **8./10.H.12.1.2.2-1** (shift)	190-024 (n=12)	16 hours post dose
	190-026 (n=436)	8.5 hours post dose
Nighttime, short-term (1-7 days) studies in non-elderly adult subjects with insomnia		
8./10.H.12.1.3.1-1 (summ) **8./10.H.12.1.3.2-1** (shift)	190-025 (n=13)	16 hours post dose
	190-045 (n=65)	5-7 days post dose
Nighttime, 2 week studies in elderly subjects with insomnia		
8./10.H.12.1.4.1-1 (summ)	190-047 (n=270)	5-7 days post dose
8./10.H.12.1.4.2-1 (shift) **8./10.H.12.1.4.3-1** (PCS – includes all post baseline laboratory assessments)	190-048 (n=231)	1-3 days post dose
Placebo-controlled, parallel group studies of 2-6 weeks duration		
8./10.H.12.2.1-1 (summ)	190-046 (n=308)	5-7 days post dose
8./10.H.12.2.2-1 (shift/age)	190-047 (n=270)	5-7 days post dose
8./10.H.12.2.2-2 (shift/race) **8./10.H.12.2.2-3** (shift/gender) **8./10.H.12.2.3-1** (thyroid shift/gender)	190-048 (n=231)	1-3 days post dose

Table VIII.J.2. Outlier Criteria for Hematology and Chemistry Parameters Employed in Selected Trials (2-Week Elderly Studies 190-047 and 190-048, 6-week Non-Elderly Study 190-046 and Longterm Non-Elderly Study 190-049).

Parameter Name (Normal Range)	PCS Low	PCS High
WBC (3.5-11.1 x 10^3/mm^3)	≤2.8 x 10^3/mm^3	≥16 x 10^3/mm^3
Neutrophils (40.0-74.0%)	≤15%	85%
Lymphocytes (19.0-48.0%)	N/A	≥75%
Monocytes (3.4-9.0%)	N/A	≥15%
Eosinophils (0.0-7.0%)	N/A	≥10%
Basophils (0.0-1.5%)	N/A	≥10%
Hemoglobin Female (11.5-15.5 g/dL) Male (13.2-17.0 g/dL)	 ≤9.5 g/dL ≤11.5 g/dL	 ≥17.5 g/dL ≥19.0 g/dL
Hematocrit Female (35.0-47.0%) Male (40.0-54.0%)	 ≤32% ≤37%	 ≥54% ≥60%
RBC (3.8-5.8 x 10^6/mm^3)	≤3.5 x 10^6/mm^3	≥6.4 x 10^6/mm^3
Platelet count (150-400 x 10^3/mm^3)	≤75 x 10^3/mm^3	≥700 x 10^3/mm^3

Parameter Name (Normal Range)	PCS Low	PCS High
Sodium (134-146 mEq/L)	≤126 mEq/L	≥156 mEq/L
Potassium (3.6-5.2 mEq/L)	≤3 mEq/L	≥6 mEq/L
Chloride (95-113 mEq/L)	≤90 mEq/L	≥118 mEq/L
Bicarbonate (20-31 mEq/L)	≤16 mEq/L	≥35 mEq/L
Calcium (8.4-10.2 mg/dL)	<8.2 mg/dL	≥12 mg/dL
Magnesium (1.4-2.1 mEq/L)	<1.2 mEq/L	>2.3 mEq/L
Inorganic phosphorous (2.4-4.9 mg/dL)	≤1.7 mg/dL	≥5.3 mg/dL
AST (0-37 U/L)(19 to <120 years)	N/A	3 x ULN
ALT (0-47 U/L)(19 to <120 years)	N/A	3 x ULN
Alkaline phosphatase (40-135 U/L) (19 to <120 years)	N/A	3 x ULN
Creatinine Female (0.5-1.0 mg/dL) (19 to <120 years) Male (0.6-1.4 mg/dL) (19 to <120 years)	N/A	≥2 mg/dL
BUN (9-24 mg/dL)	N/A	≥30 mg/dL
Total bilirubin (0.0-1.1 mg/dL)	N/A	≥ 2 mg/dL
Total protein (6.1-7.9 g/dL)	≤4.5 g/dL	≥10 g/dL
Albumin (3.7-4.9 g/dL)	≤ 2.5 g/dL	N/A
Uric Acid Female (2.2-6.4 mg/dL) Male (3.1-8.8 mg/dL)	N/A	 ≥8.5 mg/dL ≥10.5 mg/dL
Glucose (70-141 mg/dL)	≤40 mg/dL	≥175 mg/dL

Note: Normal Ranges were defined by [redacted] Individual study normal ranges may differ slightly from those defined in this table.

Table VIII.J.3 Outlier Criteria for Urinalysis and Other Laboratory Parameters Employed in Selected Trials

Parameter Name (Normal Range)	PCS Low	PCS High
Protein (Negative)	N/A	>2+
Ketones (Negative)	N/A	4 +
Glucose (Normal)	N/A	4 +

Parameter Name (Normal Range)	PCS Low	PCS High
T_3 uptake (24.0- 35.0%)	<24.0 %TU	>35.0 %TU
T_4 (4.5-12.5 µg/dL)	<4.5 µg/dL	>12.5 µg/dL
TSH (0.400-4.000 µIU/mL)	<0.4 µIU/mL	>4.0 µIU/mL

Note: Normal Ranges were defined by Individual study normal ranges may differ slightly from those defined in this table.

Estradiol Outlier Values (only conducted in Studies 190-046, -048 and –049)

Estradiol Classification	Estradiol Reference Range (pg/mL)
Ovulating Females	
Follicular Phase	0-160
Luteal Phase	27-246
Peri-ovulatory Phase	34-400
Post-Menopausal Females	0-30
Females Taking Oral Contraceptives/Hormone Replacement Therapy	0-102
Males	0-56

Note: Normal Ranges were defined by

Table VIII.J.4. Study 190-049. Double-Blind Phase

Mean (± Standard Deviation) Changes from Baseline to the End of the Study for Hematology and Serum Chemistry Parameters in the Nighttime, 6-Month (Double-blind) Study in Non-Elderly Subjects with Insomnia (Safety Population)

Parameter (Units)	Placebo (N=195)	Esopiclone				
		1 mg (N=0)	2 mg (N=0)	2.5 mg (N=0)	3 mg (N=593)	≥3.5 mg (N=0)
Hematology						
WBC ($x10^3/mm^3$)	-0.1 (1.59)	-	-	-	-0.2 (1.85)	-
Neutrophils (%)	0.1 (7.07)	-	-	-	-0.4 (8.05)	-
Lymphocytes (%)	-0.4 (6.04)	-	-	-	0.0 (6.83)	-
Monocytes (%)	0.2 (1.29)	-	-	-	0.1 (1.50)	-
Eosinophils (%)	0.2 (1.43)	-	-	-	0.2 (2.03)	-
Basophils (%)	0.0 (0.64)	-	-	-	0.0 (0.61)	-
Hemoglobin (g/dL)	-0.3 (0.80)	-	-	-	-0.3 (0.77)	-
RBC ($x10^6/mm^3$)	0.0 (0.24)	-	-	-	-0.1 (0.26)	-
Platelet count ($x10^3/mm^3$)	4.8 (41.44)	-	-	-	-0.8 (43.93)	-
Serum Chemistry						
Sodium (mEq/L)	-0.8 (2.65)	-	-	-	-0.8 (2.39)	-
Potassium (mEq/L)	0.0 (0.40)	-	-	-	0.0 (0.40)	-
Chloride (mEq/L)	-1.1 (2.94)	-	-	-	-1.4 (2.74)	-
Bicarbonate (mEq/L)	-0.3 (2.21)	-	-	-	0.1 (2.27)	-
Calcium (mg/dL)	-0.2 (0.46)	-	-	-	-0.2 (0.43)	-
Magnesium (mEq/L)	-0.1 (0.12)	-	-	-	-0.1 (0.13)	-
Inorganic phosphorus (mg/dL)	0.0 (0.63)	-	-	-	0.0 (0.58)	-
AST (U/L)	1.1 (9.42)	-	-	-	-0.5 (8.33)	-
ALT (U/L)	1.3 (13.77)	-	-	-	-0.7 (12.51)	-
Alkaline phosphatase (U/L)	-0.1 (12.54)	-	-	-	-1.2 (12.72)	-
Creatinine (mg/dL)	0.0 (0.11)	-	-	-	0.1 (0.13)	-
BUN (mg/dL)	0.3 (3.23)	-	-	-	0.1 (3.65)	-
Total bilirubin (mg/dL)	0.0 (0.20)	-	-	-	0.0 (0.19)	-
Total protein (g/dL)	-0.2 (0.41)	-	-	-	-0.2 (0.37)	-
Albumin (g/dL)	-0.1 (0.22)	-	-	-	-0.1 (0.22)	-
Uric acid (mg/dL)	0.1 (0.80)	-	-	-	0.1 (0.83)	-
Glucose (mg/dL)	4.6 (19.81)	-	-	-	4.4 (22.85)	-

Note: Study 190-049 was included.

Note: Baseline was the closest non-missing value preceding the first dose. The end of the study was the last non-missing laboratory result from the double-blind treatment period.

Reference: EOT Table 11.1.

Table VIII.J.5. Study 190-049 Double-blind Phase.
PCS Laboratory Values that Occurred During the 6-Month Double-blind Period (Safety Population)

Parameter	Treatment	PCS Low n (%)	PCS High n (%)
Hematology			
Total WBC count	Placebo	4 (2.1)	0 (0.0)
Total WBC count	Esopiclone 3 mg	7 (1.2)	4 (0.7)
Neutrophils	Placebo	1 (0.5)	1 (0.5)
Neutrophils	Esopiclone 3 mg	0 (0.0)	3 (0.5)
Monocytes	Placebo	0 (0.0)	1 (0.5)
Monocytes	Esopiclone 3 mg	0 (0.0)	2 (0.3)
Eosinophils	Placebo	0 (0.0)	6 (3.1)
Eosinophils	Esopiclone 3 mg	0 (0.0)	9 (1.5)
Hemoglobin (female)	Placebo	1 (0.5)	0 (0.0)
Hemoglobin (female)	Esopiclone 3 mg	4 (0.7)	0 (0.0)
Hemoglobin (male)	Placebo	1 (0.5)	0 (0.0)
Hemoglobin (male)	Esopiclone 3 mg	2 (0.3)	0 (0.0)
RBC count	Placebo	1 (0.5)	0 (0.0)
RBC count	Esopiclone 3 mg	2 (0.3)	1 (0.2)
Platelet count	Placebo	0 (0.0)	1 (0.5)
Platelet count	Esopiclone 3 mg	0 (0.0)	2 (0.3)
Chemistry			
Glucose	Placebo	0 (0.0)	9 (4.6)
Glucose	Esopiclone 3 mg	0 (0.0)	17 (2.9)
Potassium	Placebo	2 (1.0)	0 (0.0)
Potassium	Esopiclone 3 mg	2 (0.3)	2 (0.3)
Magnesium	Esopiclone 3 mg	0 (0.0)	1 (0.2)
Calcium	Esopiclone 3 mg	0 (0.0)	1 (0.2)
Inorganic Phosphorus	Placebo	0 (0.0)	2 (1.0)
Inorganic Phosphorus	Esopiclone 3 mg	1 (0.2)	12 (2.0)
Bicarbonate	Placebo	0 (0.0)	1 (0.5)
AST (SGOT)	Esopiclone 3 mg	0 (0.0)	3 (0.5)
ALT (SGPT)	Esopiclone 3 mg	0 (0.0)	1 (0.2)
Alkaline phosphatase	Placebo	0 (0.0)	1 (0.5)
Creatinine (male)	Esopiclone 3 mg	0 (0.0)	1 (0.2)

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Table VIII.J.5, continued.
Study 190-049 Double-Blind Phase.

PCS Laboratory Values that Occurred During the 6-Month Double-blind Period (Safety Population)

Parameter	Treatment	PCS Low n (%)	PCS High n (%)
Chemistry (continued)			
Total bilirubin	Placebo	0 (0.0)	6 (3.1)
Total bilirubin	Esopiclone 3 mg	0 (0.0)	6 (1.0)
Uric acid (female)	Placebo	0 (0.0)	1 (0.5)
Uric acid (female)	Esopiclone 3 mg	0 (0.0)	8 (1.3)
Uric acid (male)	Esopiclone 3 mg	0 (0.0)	6 (1.0)
Hormone Assessments			
T3 uptake	Placebo	3 (1.5)	28 (14.4)
T3 uptake	Esopiclone 3 mg	18 (3.0)	104 (17.5)
T4	Placebo	3 (1.5)	2 (1.0)
T4	Esopiclone 3 mg	7 (1.2)	17 (2.9)
TSH	Placebo	11 (5.6)	11 (5.6)
TSH	Esopiclone 3 mg	42 (7.1)	29 (4.9)
Urinalysis			
Urine blood	Placebo	0 (0.0)	12 (6.2)
Urine blood	Esopiclone 3 mg	0 (0.0)	38 (6.4)
Urine protein	Placebo	0 (0.0)	21 (10.8)
Urine protein	Esopiclone 3 mg	0 (0.0)	74 (12.5)
Urine glucose	Placebo	0 (0.0)	9 (4.6)
Urine glucose	Esopiclone 3 mg	0 (0.0)	20 (3.4)

Note: This table summarizes data for Population A + C, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: PCS low and high values were defined by Sepracor.

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Table VIII.J.6. Study 190-049 Open-Label Phase (Continued on next page)
PCS Laboratory Values that Occurred During the 6-Month Open-label Period by Previous Double-blind Treatment (Safety Population)

Parameter	Previous Double-blind Treatment	PCS Low n (%)	PCS High n (%)
Hematology			
Total WBC count	Placebo	1 (0.9)	0 (0.0)
Total WBC count	Esopiclone 3 mg	8 (2.2)	1 (0.3)
Neutrophils	Placebo	1 (0.9)	2 (1.8)
Neutrophils	Esopiclone 3 mg	3 (0.8)	2 (0.6)
Monocytes	Esopiclone 3 mg	0 (0.0)	6 (1.7)
Eosinophils	Placebo	0 (0.0)	6 (5.4)
Eosinophils	Esopiclone 3 mg	0 (0.0)	12 (3.3)
Hemoglobin (female)	Esopiclone 3 mg	1 (0.3)	0 (0.0)
Hemoglobin (male)	Placebo	2 (1.8)	0 (0.0)
Hemoglobin (male)	Esopiclone 3 mg	1 (0.3)	0 (0.0)
RBC count	Placebo	1 (0.9)	0 (0.0)
RBC count	Esopiclone 3 mg	1 (0.3)	1 (0.3)
Platelet count	Esopiclone 3 mg	1 (0.3)	0 (0.0)
Chemistry			
Glucose	Placebo	0 (0.0)	6 (5.4)
Glucose	Esopiclone 3 mg	0 (0.0)	11 (3.1)
Potassium	Esopiclone 3 mg	2 (0.6)	0 (0.0)
Chloride	Placebo	1 (0.9)	0 (0.0)
Calcium	Placebo	2 (1.8)	0 (0.0)
Calcium	Esopiclone 3 mg	3 (0.8)	1 (0.3)
Inorganic Phosphorus	Placebo	0 (0.0)	2 (1.8)
Inorganic Phosphorus	Esopiclone 3 mg	1 (0.3)	6 (1.7)
Bicarbonate	Placebo	1 (0.9)	0 (0.0)
AST (SGOT)	Esopiclone 3 mg	0 (0.0)	1 (0.3)
ALT (SGPT)	Esopiclone 3 mg	0 (0.0)	3 (0.8)
Creatinine (male)	Esopiclone 3 mg	0 (0.0)	1 (0.3)
Total bilirubin	Placebo	0 (0.0)	3 (2.7)
Total bilirubin	Esopiclone 3 mg	0 (0.0)	6 (1.7)
Uric acid (female)	Esopiclone 3 mg	0 (0.0)	8 (2.2)

Table VIII.J.6 continued.
Study 190-049 Open-Label Phase
PCS Laboratory Values that Occurred During the 6-Month Open-label Period by Previous Double-blind Treatment (Safety Population)

Parameter	Previous Double-blind Treatment	PCS Low n (%)	PCS High n (%)
Hormone Assessments			
T3 uptake	Placebo	5 (4.5)	14 (12.6)
T3 uptake	Esopiclone 3 mg	18 (5.0)	72 (20.0)
T4	Placebo	2 (1.8)	4 (3.6)
T4	Esopiclone 3 mg	6 (1.7)	13 (3.6)
TSH	Placebo	6 (5.4)	7 (6.3)
TSH	Esopiclone 3 mg	29 (8.1)	29 (8.1)
Urinalysis			
Urine blood	Placebo	0 (0.0)	8 (7.2)
Urine blood	Esopiclone 3 mg	0 (0.0)	29 (8.1)
Urine protein	Placebo	0 (0.0)	13 (11.7)
Urine protein	Esopiclone 3 mg	0 (0.0)	45 (12.5)
Urine glucose	Placebo	0 (0.0)	6 (5.4)
Urine glucose	Esopiclone 3 mg	0 (0.0)	20 (5.6)

Note: This table summarizes data for Population B + D, see Figures 9.7.1.2-1 and 10.1-2 for the description of the populations.

Note: All subjects received esopiclone 3 mg during the open-label period.

Note: PCS low and high values were defined by Sepracor.

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Tables VIII.J.7 Panels A-E on Laboratory Parameters of Special Interest

Panel A. Mean (±SD) Change from Baseline to the End of the Study (5-7 Days After Treatment) for Hormonal Levels in the 6-Week Non-elderly Chronic Insomnia Patient Study (190-046)

Parameter (Units)	Placebo (N=99)	Esopiclone 1 mg (N=0)	Esopiclone 2 mg (N=104)	Esopiclone 2.5 mg (N=0)	Esopiclone 3 mg (N=105)	Esopiclone ≥3.5 mg (N=0)
Thyroid Function						
T_3 uptake (%)	1.6 (2.48)	-	1.7 (2.32)	-	1.8 (1.93)	-
T_4 (µg/dL)	0.4 (1.16)	-	0.3 (1.41)	-	0.2 (1.09)	-
TSH (µIU/mL)	0.0 (0.49)	-	-0.1 (0.82)	-	0.1 (1.25)	-

Note: Study 190-046 was included.
Note: Baseline was the closest non-missing value preceding the first dose. The end of the study was the last non-missing laboratory result from the study exit visit.
Reference: EOT Table 11.1.

Panel B. The Incidence of Outliers on Hormonal Levels (obtained at baseline and 5-7 days after treatment) in the 6-Week Non-elderly Chronic Insomnia Patient Study (190-046)

Parameter (Units)	Placebo (N=99)		Esopiclone 1 mg (N=0)		Esopiclone 2 mg (N=104)		Esopiclone 2.5 mg (N=0)		Esopiclone 3 mg (N=105)		Esopiclone ≥3.5 mg (N=0)	
	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High
Thyroid Function												
T_3 uptake (%)	3 (3.0)	11 (11.1)	-	-	0 (0.0)	13 (12.5)	-	-	3 (2.9)	6 (5.7)	-	-
T_4 (µg/dL)	0 (0.0)	1 (1.0)	-	-	1 (1.0)	2 (1.9)	-	-	0 (0.0)	0 (0.0)		
TSH (µIU/mL)	1 (1.0)	4 (4.0)	-	-	1 (1.0)	9 (8.7)	-	-	3 (2.9)	12 (11.4)	-	-

Note: Study 190-046 was included.
Note: Subjects were counted once per PCS criteria.
Note: The assignment of a PCS category was based upon all post-baseline data.
Reference: EOT Table 14.

Panel C. Mean (±SD) Change from Baseline to the End of the Study (last non-missing value from the double-blind treatment phase) for Hormonal Levels in the 6-Month Double-blind Treatment Phase in the Longterm Non-elderly Chronic Insomnia Patient Study (190-049)

Parameter (Units)	Placebo (N=195)	Esopiclone 1 mg (N=0)	Esopiclone 2 mg (N=0)	Esopiclone 2.5 mg (N=0)	Esopiclone 3 mg (N=593)	Esopiclone ≥3.5 mg (N=0)
Thyroid Function						
T_3 uptake (%)	2.0 (2.76)	-	-	-	2.1 (2.78)	-
T_4 (µg/dL)	-0.1 (1.37)	-	-	-	-0.1 (1.31)	-
TSH (µIU/mL)	0.1 (1.29)	-	-	-	-0.1 (0.72)	-

Note: Study 190-049 was included.
Note: Baseline was the closest non-missing value preceding the first dose. The end of the study was the last non-missing laboratory result from the double-blind treatment period.
Reference: EOT Table 11.1.

Panel D. The Incidence of Outliers for Hormonal Levels in the 6-Month Double-blind Treatment Phase in the Longterm Non-elderly Chronic Insomnia Patient Study (190-049)

Parameter (Units)	Placebo (N=195)		Esopiclone 1 mg[a] (N=0)		Esopiclone 2 mg (N=0)		Esopiclone 2.5 mg (N=0)		Esopiclone 3 mg (N=593)		Esopiclone ≥3.5 mg (N=0)	
	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High	PCS Low	PCS High
Hematology n (%)												
T_3 uptake (%)	3 (1.5)	28 (14.4)	-	-	-	-	-	-	18 (3.0)	104 (17.5)	-	-
T_4 (µg/dL)	3 (1.5)	2 (1.0)	-	-	-	-	-	-	7 (1.2)	17 (2.9)		
TSH (µIU/mL)	11 (5.6)	11 (5.6)	-	-	-	-	-	-	42 (7.1)	29 (4.9)	-	-

Note: Study 190-049 was included.
Note: Subjects were counted once per PCS criteria.
Note: The assignment of a PCS category was based upon all post-baseline data.
Reference: EOT Table 14.

continued on next page.

Tables VIII.J.7 (Panels A-E), Continued.

Laboratory Parameters of Special Interest

Panel E.

Mean (± Standard Deviation) Changes from Baseline to the End of the Study for Hormone Function in the Nighttime, 6-Month, Double-blind Study in Non-Elderly Adult Subjects with Insomnia (Safety Population)

Parameter (Units)	Statistic	Placebo (N=195)	Esopiclone 1 mg (N=0)	Esopiclone 2 mg (N=0)	Esopiclone 2.5 mg (N=0)	Esopiclone 3 mg (N=593)	Esopiclone ≥3.5 mg (N=0)
Hormone Function							
Estradiol (pg/mL)							
Post-Menopausal Females	N	32	-	-	-	91	-
	Baseline Mean	30.5				41.6	
	Mean Change (SD)	7.3 (37.89)				-6.6 (42.85)	
Females Taking Oral Contraceptives/Hormone Replacement Therapy	N	42	-	-	-	133	-
	Baseline Mean	56.7				53.5	
	Mean Change (SD)	-1.7 (52.23)				-0.4 (76.11)	
Males	N	70	-	-	-	219	-
	Baseline Mean	24.1				21.8	
	Mean Change (SD)	3.0 (11.84)				4.9 (10.55)	

Note: Study 190-049 was included.
Note: Baseline was the closest non-missing value preceding the first dose. The end of the study was the last non-missing laboratory result from the double-blind treatment period.
Note: Estradiol values collected as "<2", "<5", and "<15" pg/mL were analyzed as 1.99, 4.99, and 14.99, respectively.
Note: For estradiol, each subject was counted once in the applicable estradiol classification.
Note: Changes were not calculated for the follicular phase, luteal phase, peri-ovulatory phase, or unassigned category because ovulating subjects were not necessarily in the same phase at baseline and at the end of the double-blind treatment period.
Reference: EOT Table 11.2.

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Table VIII.K1. Outlier Criteria for Vital Sign and Other Safety Parameters.

Parameter Name	Low	Decrease from Baseline	High	Increase from Baseline
Systolic BP	<90 mm Hg	≥20 mmHg	>180 mm Hg	≥20 mmHg
Diastolic BP	<50 mm Hg	≥15 mmHg	>105 mm Hg	≥15 mmHg
Heart rate	<50 bpm	≥15 bpm	>120 bpm	≥15 bpm
Respiration rate	<10 breaths/min	≥50%	>25 breaths/min	≥50%
Temperature	N/A	≥2° F	101° F	≥2° F
Weight	N/A	≥7%	N/A	≥7%

Notes: PCS = Potentially Clinically Significant.

A vital sign value was PCS abnormal if it was below the specified lower limit **and** decreased from baseline **or** it was above the specified upper limit **and** increased from baseline.

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Table VIII.K2. Vital Sign Data Collection Time-Points used for ISS Summary Tables

In Text Table Numbers	Studies in Analysis	Analysis Assessment Timepoint per Study
Daytime, short-term (1-7 days) studies in healthy volunteers		
8./10.H.13.1.1.1-1 (summ) **8./10.H.13.1.1.2-1** (PCS*) ***PCS** includes all post-baseline vital sign assessments (including unscheduled)	190-001 (n=108)	2 days post dose
	190-002 (n=48)	2 days post dose
	190-005 (n=36)	2 days post dose
	190-010 (n=18)	2 days post dose
	190-011 (n=79)	1 day post dose
	190-012 (n=14)	6 hours post dose
	190-015 (n=24)	1 day post dose
	190-018 (n=40)	3 days post dose
	190-019 (n=36)	1 day post dose
	190-020 (n=40)	1 day post dose
	190-021 (n=12)	6-20 days post dose
	190-023 (n=18)	2 days post dose
Nighttime, short-term (1-7 days) studies in non-elderly adult healthy volunteers		
8./10.H.13.1.2.1-1 (summ) **8./10.H.13.1.2.2-1** (PCS*) ***PCS** includes all post-baseline vital sign assessments (including unscheduled)	190-024 (n=12)	16 hours post dose
	190-026 (n=436)	8.5 hours post dose
Nighttime, short-term (1-7 days) studies in non-elderly adult subjects with insomnia		
8./10.H.13.1.3.1-1 (summ) **8./10.H.13.1.3.2-1** (PCS*) ***PCS** includes all post-baseline vital sign assessments (including unscheduled)	190-025 (n=13)	16 hours post dose
	190-045 (n=65)	8 hours post dose
Nighttime, 2 week studies in elderly subjects with insomnia		
8./10.H.13.1.4.1-1 (summ) **8./10.H.13.1.4.2-1** (PCS*) ***PCS** includes all post-baseline vital sign assessments (including unscheduled)	190-047 (n=270)	8 hours post dose
	190-048 (n=231)	8-48 hours post dose

Table VIII.L3. ECG Data Collection "End-of-Treatment" Time-Points used for ISS Summary Tables

In Text Table Numbers	Studies in Analysis	Analysis Assessment Timepoint per Study
Daytime, short-term (1-7 days) studies in healthy volunteers (Central-Read Results)		
8./10.H.14.1.1.1-1 (summ)	190-002 (n=48)	90 min. post dose, day 6
	190-005 (n=36)	2 days post dose
	190-011 (n=70)	1 day post dose
Daytime, short-term (1-7 days) studies in healthy adult volunteers (Investigator-Read Results)		
8./10.H.14.1.1.2-1 (summ)	190-001 (n=108)	2 days post dose
	190-010 (n=18)	2 days post dose
	190-012 (n=14)	Up to 7 days post dose
	190-015 (n=24)	1 day post dose
	190-018 (n=40)	3 days post dose
	190-019 (n=36)	1 day post dose
	190-020 (n=40)	1 day post dose
	190-021 (n=12)	6-20 days post dose
	190-023 (n=18)	2 days post dose
Nighttime, short-term (1-7 days) studies in non-elderly adult healthy volunteers (Investigator-Read Results)		
End of Text Table 18.1 (No in-text table) (summ)	190-024 (n=12)	16 hours post dose
	190-026 (n=436)	10.5 – 11.5 hours post dose
Placebo-controlled, parallel group studies of 2-6 weeks duration (Central-Read Results)		
8./10.H.14.1.7-1 (summ)	190-046 (n=308)	5-7 days post dose
	190-048 (n=231)	1-3 days post dose

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Tables VIII.L4 and 5- Studies 190-002, 190-005 and 190-011 (Phase I Trials with 90 Minute Post-dose ECGs)

Table VIII.L4.

Summary of Central-Read ECG Results at 90 Minutes Post-Dose on Day 1 by Treatment (Safety Population)

Parameter (Units)	Placebo (N=24)	Esopiclone 1 mg (N=18)	Esopiclone 2 mg (N=46)	Esopiclone 2.5 mg (N=0)	Esopiclone 3 mg (N=57)	Esopiclone ≥3.5 mg (N=18)
P-R Interval (ms)						
Baseline mean (SD)	164.2 (21.32)	157.8 (18.87)	158.1 (17.12)	-	155.3 (17.07)	158.1 (15.63)
Mean (SD) change	-0.5 (12.04)	0.6 (11.07)	-0.8 (11.65)	-	-3.6 (9.71)	2.7 (14.20)
QRS Duration (ms)						
Baseline mean (SD)	91.7 (7.65)	86.9 (7.04)	89.8 (6.99)	-	86.9 (7.09)	89.0 (6.44)
Mean (SD) change	-2.0 (6.81)	-1.4 (6.99)	0.6 (4.89)	-	-0.8 (4.87)	0.4 (5.42)
QT Interval (ms)						
Baseline mean (SD)	391.3 (28.15)	380.4 (26.17)	386.1 (25.01)	-	382.0 (20.65)	377.9 (23.33)
Mean (SD) change	2.1 (13.79)	-0.6 (18.25)	5.0 (16.72)	-	0.8 (11.90)	-1.5 (13.54)
R-R Interval (ms)						
Baseline mean (SD)	1004.3 (160.33)	974.6 (160.81)	989.5 (115.90)	-	981.5 (149.26)	948.3 (143.03)
Mean (SD) change	30.1 (99.64)	5.1 (93.05)	56.9 (106.97)	-	21.1 (100.51)	-4.2 (101.10)
QT_{C-B} (ms)						
Baseline mean (SD)	392.3 (23.86)	388.0 (27.38)	389.4 (19.49)	-	388.1 (23.24)	390.3 (24.14)
Mean (SD) change	-4.2 (18.59)	-1.7 (22.61)	-5.8 (14.47)	-	-3.0 (14.95)	0.1 (15.39)
QT_{C-F} (ms)						
Baseline mean (SD)	391.7 (21.53)	385.1 (22.22)	388.1 (18.48)	-	385.8 (18.03)	385.9 (19.15)
Mean (SD) change	-2.1 (14.75)	-1.3 (19.26)	-2.2 (11.89)	-	-1.8 (10.87)	-0.5 (10.58)

Note: Central read data for Studies 190-002 and 190-005 were collected at 90 minutes post-dose on Day 1. For Study 190-011, Day 1 measurements were collected in both Periods 1 and 2, and because the same dose of study drug was administered in each period, the average of the baseline values and the average change from baseline to Day 1 was used in this presentation. Baseline was the closest non-missing value preceding the first dose.
Reference: EOT Table 22.1.

Table VIII.L5. Summary of Central Read ECG Results at 90 Minutes Post-Dose on Day 6 (for Study 190-022) or Day 7 (for Study 190-005) of Treatment

Parameter (Units)	Placebo (N=24)	Esopiclone 1 mg (N=18)	Esopiclone 2 mg (N=6)	Esopiclone 2.5 mg (N=0)	Esopiclone 3 mg (N=18)	Esopiclone ≥3.5 mg (N=18)
P-R Interval (ms)						
Baseline mean (SD)	164.2 (21.32)	157.8 (18.87)	156.8 (27.48)	-	160.7 (19.49)	158.1 (15.63)
Mean (SD) change	0.1 (12.19)	1.1 (11.27)	4.2 (20.90)	-	-5.8 (11.91)	1.0 (10.95)
QRS Duration (ms)						
Baseline mean (SD)	91.7 (7.65)	86.9 (7.04)	91.2 (7.83)	-	90.6 (9.94)	89.0 (6.44)
Mean (SD) change	-2.8 (5.58)	4.8 (6.33)	-4.8 (4.62)	-	-2.2 (7.29)	-0.4 (7.41)
QT Interval (ms)						
Baseline mean (SD)	391.3 (28.15)	380.4 (26.17)	394.0 (30.36)	-	387.1 (23.07)	377.9 (23.33)
Mean (SD) change	-6.5 (19.55)	-10.0 (26.12)	-5.3 (23.18)	-	-11.1 (20.76)	-11.7 (22.14)
R-R Interval (ms)						
Baseline mean (SD)	1004.3 (160.33)	974.6 (160.81)	987.0 (171.21)	-	986.8 (150.68)	948.3 (143.03)
Mean (SD) change	-46.2 (143.76)	-62.9 (150.94)	31.3 (140.76)	-	-77.7 (158.37)	-78.7 (167.10)
QT_{C-B} (ms)						
Baseline mean (SD)	392.3 (23.86)	388.0 (27.38)	398.6 (20.51)	-	392.1 (28.88)	390.3 (24.14)
Mean (SD) change	2.1 (21.51)	1.6 (19.90)	-12.1 (16.90)	-	3.1 (16.33)	4.7 (25.13)
QT_{C-F} (ms)						
Baseline mean (SD)	391.7 (21.53)	385.1 (22.22)	396.8 (17.72)	-	390.2 (23.24)	385.9 (19.15)
Mean (SD) change	-0.8 (16.07)	-2.3 (17.52)	-9.7 (12.94)	-	-1.6 (9.69)	-1.0 (17.05)

Note: Central read data for Studies 190-002 and 190-005 were collected at 90 minutes post-dose at steady state (Day 6 and Day 7, respectively). Baseline was the closest non-missing value preceding the first dose.
Reference: EOT Table 22.2.

Table VIII.L6.

Summary of Central-Read ECG Results at 90 Minutes Post-Dose Overall by Treatment (Safety Population)

Parameter (Units)	Placebo (N=24)	Esopiclone 1 mg (N=18)	Esopiclone 2 mg (N=46)	Esopiclone 2.5 mg (N=0)	Esopiclone 3 mg (N=57)	Esopiclone ≥3.5 mg (N=18)
P-R Interval (ms)						
Baseline mean (SD)	164.2 (21.32)	157.8 (18.87)	158.1 (17.12)	-	155.3 (17.07)	158.1 (15.63)
Mean (SD) change	1.0 (10.07)	1.7 (9.54)	-0.8 (12.06)	-	-3.2 (8.48)	-0.3 (9.94)
95% CI	-3.3, 5.4	-3.2, 6.6	-4.4, 2.8	-	-5.4, -0.9	-5.3, 4.6
QRS Duration (ms)						
Baseline mean (SD)	91.7 (7.65)	86.9 (7.04)	89.8 (6.99)	-	86.9 (7.09)	89.0 (6.44)
Mean (SD) change	-1.5 (4.78)	2.2 (5.67)	0.4 (4.58)	-	-0.9 (4.59)	0.4 (4.90)
95% CI	-3.6, 0.5	-0.7, 5.1	-1.0, 1.7	-	-2.2, 0.3	-2.1, 2.8
QT Interval (ms)						
Baseline mean (SD)	391.3 (28.15)	380.4 (26.17)	386.1 (25.01)	-	382.0 (20.65)	377.9 (23.33)
Mean (SD) change	-4.8 (14.51)	-8.7 (19.91)	4.2 (16.11)	-	-2.4 (13.93)	-9.3 (18.97)
95% CI	-11.1, 1.5	-19.0, 1.5	-0.5, 9.0	-	-6.1, 1.3	-18.7, 0.2
R-R Interval (ms)						
Baseline mean (SD)	1004.3 (160.33)	974.6 (160.81)	989.5 (115.90)	-	981.5 (149.26)	948.3 (143.03)
Mean (SD) change	-33.3 (122.89)	-56.4 (110.58)	51.7 (105.59)	-	0.2 (120.22)	-59.3 (121.65)
95% CI	-86.4, 19.9	-113.3, 0.4	20.3, 83.0	-	-31.7, 32.1	-119.8, 1.2
QT_{C-B} (ms)						
Baseline mean (SD)	392.3 (23.86)	388.0 (27.38)	389.4 (19.49)	-	388.1 (23.24)	390.3 (24.14)
Mean (SD) change	1.3 (17.71)	1.9 (18.89)	-5.6 (13.89)	-	-2.1 (14.51)	3.0 (15.41)
95% CI	-6.4, 9.0	-7.9, 11.6	-9.8, -1.5	-	-5.9, 1.8	-4.6, 10.7
QT_{C-F} (ms)						
Baseline mean (SD)	391.7 (21.53)	385.1 (22.22)	388.1 (18.48)	-	385.8 (18.03)	385.9 (19.15)
Mean (SD) change	-0.7 (12.76)	-1.7 (16.50)	-2.3 (11.10)	-	-2.2 (9.49)	-1.3 (11.50)
95% CI	-6.3, 4.8	-10.2, 6.7	-5.6, 1.0	-	-4.7, 0.3	-7.0, 4.5

Note: Overall summary statistics by treatment were calculated using the mean value (or mean change) across all post-baseline assessments at 90 minutes post-dose for a subject. Central read data were collected at 90 minutes post-dose on Days 1-6 for Study 190-002 (Period 2), Days 1 and 7 for Study 190-005, and Day 1 in Periods 1 and 2 for Study 190-011. Baseline was the closest non-missing value preceding the first dose (for Study 190-002, baseline was defined relative to the first dose in Period 2).

Reference: EOT Table 22.4.

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Attachment 1.

The below is a listing of some additional areas that would potentially need further clarification or inquiry, if the NDA were to be given an approvable status by the agency:

1. The submission also does not describe any past foreign applications on ESZ, although this is not explicitly stated (only reference is made to "active" submissions). Perhaps, this should be clarified.
2. Further clarification is needed from the sponsor regarding the disposition categories of "other" and "voluntary withdrawal." Also clarification on how efficacy data was handled from these subjects is needed.
3. Results on the disposition of subjects in Study 190-047 showed a higher incidence of subjects who voluntarily withdrew for any reason in the 2 mg ESZ group (11.4%) than in the placebo group (8.8%). The incidence in the 1 mg ESZ group was 6.9%. Surprisingly, a numerically greater percentage of placebo subjects withdrew from the study due to an adverse event (6.3%) compared to on 1.4% and 2.5% in the 1 mg and 2 mg ESZ groups, respectively. Another atypical finding was a somewhat large incidence of subjects who withdrew voluntarily in the 2 mg ESZ group (8.9%) compared to the low dose ESZ group and the placebo group (2.8% and 2.5%, respectively). An explanation for these atypical results cannot be found in the study report (the corrected version of the study report, as provided in an amendment submission dated 3/25/03).
4. Study 190-046 is described as a 6-week trial showing efficacy in proposed labeling, yet the PSG data from which primary efficacy results were obtained was only collected out to Day 29 of treatment. Therefore, claims based on PSG results could not refer to a 6-week period, but would need to specifically state the duration that they actually reflect.
5. Hepatomegaly and liver damage ADOs were each reported in one ESZ S and no placebo subjects. It is not clear to this reviewer why the AE of liver damage was not classified as an SAE.
6. According to the study report of 190-046 in the submission, the original protocol included a Visit 3 for PSG recording during the double-blind treatment phase of the study (the time point for Visit 3 was not specified in the submission). However, Visit 3 was later deleted in a protocol amendment dated February 28, 2001 (as described on page 51 of the 190-046.pdf file; the study report file). The rationale for this protocol amendment could not be found in the submission.
7. The majority of subjects (66% of subjects) in Study 190-046 were identified as having "important" protocol deviations and it is not clear if data from these subjects were included in the primary analyses. 90% of subjects were reported to be completers yet on p. 25 of CSR protocol violators resulted in withdrawal from the study (it is not clear if the numbers match, since protocol violators are generally withdrawn from the study prematurely).
8. The incidence of gender specific AEs did not appear to be calculated using the correct gender appropriate number of subjects in the denominator. For example refer to the table on page 78 of the 190-046.pdf showing that 2 or 1.9% of subjects had dysmennorhea, yet if calculated using 66 women as the denominator one obtains the value of 3%. All studies need to show the incidence of gender specific AEs using the correct gender appropriate denominator.
9. It is not clear if there were any fatal overdoses exclusively involving zopiclone overdose and what the cause of death and the signs and symptoms leading to death were in these cases.
10. Differences between investigator listings were observed as previously described in this review (see Section V).
11. Descriptive statistical results of baseline efficacy and safety measures could not be found for most measures for each treatment group for most of the trials.
12. The two PSG trials that examined rebound effects (Studies 190-046 and 190-047) conducted PSGs on each rebound night (Nights is 1 and 2 after cessation of double-blind treatment). Yet, results on potential rebound effects on sleep architecture could not be found in these trials.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Brugge
9/15/03 03:42:31 PM
MEDICAL OFFICER
Recommend that it not be approved (and not be given approvable status)
Paul: This is the complete review. By accident I DFSed my appendix earlier today, so please delete my previous DFSed "review" under this NDA

Paul Andreason
11/7/03 02:24:17 PM
MEDICAL OFFICER
I recommend a non-approvable action. See my memo to file dated November 7, 2003