Design
This was a multicenter, double- blind, placebo- controlled, randomized, parallel- group study to investigate the short- term (1- night) safety and tolerability of a single dose of zaleplon (5 or 10 mg) and its effectiveness as a hypnotic in healthy subjects. The treatment arms were balanced and subjects were randomly assigned consecutively at each study center.

Assessments
The schedule of assessments and events may be found in the appendix in table 7.2.6.1.2.

Analysis Plan
The primary efficacy variable is latency to persistent sleep (LPS). Sleep questionnaire data was also collected that included TSO, TTS, and NAW.

Patient Disposition
Four hundred twenty- three (423) subjects entered the initial screening phase. Two hundred sixty- eight (268) subjects were randomly assigned to one of the 3 treatment groups. One (1) subject (21038- 0057) was considered a "no- data" subject. This subject was considered potentially exposed to drug treatment; double- blind study medication (zaleplon 5 mg) was dispensed to the subject at the sleep laboratory, but only the screening log and drug supply data are available; no CRF or source documents are available. No data on this subject are included in the database, and the subject is not included in either the safety or efficacy analysis.

The remaining 267 subjects who received randomly assigned study medication under double- blind conditions were included in all safety analyses. Three (3) of these 267 subjects did not meet ITT criteria, and therefore were excluded from the ITT efficacy analysis.

Baseline Demographics/Severity of Illness
Subjects baseline demographics are listed in table 7.2.6.1.3 in the appendix. The percentages of women in the zaleplon treatment groups are statistically significantly different from placebo ($p=0.02$). There are no differences in either age or ethnicity. Weight trends toward significance; however, the mean differences in weight amongst the three treatment groups is $\pm$ 2 Kg. Subjects were screened as healthy volunteers so no measures of difference of illness was made.

Concomitant Medications

Concomitant medications during double blind therapy are listed in table 7.2.1.6.4.

Table 7.2.6.1.4 Concomitant therapies in study 210-US

Medication Class	Placebo	Zaleplon 5 mg	Zaleplon 10 mg
Total subjects with concomitant medications	22 (25)	31 (35)	29 (32)
Hormones (estrogen replacement)			
estrogens	5 (6)	4 (5)	3 (3)
progestogens and estrogens, fixed combinations			
Propionic acid derivatives	5 (6)	9 (10)	7 (8)
Multivitamins, other combinations	2 (2)	5 (6)	5 (6)
	2 (2)	5 (6)	2 (2)

Efficacy Results

Nonparametric methods were used for the primary analyses because of indications that the assumptions for the normal theory analysis were violated. Table 7.2.6.1.5 the median difference in LPS for zaleplon and placebo with results of Dunnett's Test.

Table 7.2.6.1.5 LPS (minutes) ITT subjects OC analysis on ranked data study 210-US

			p-value differences from Zaleplon		
Treatment Group	n	Median	5 mg	10 mg	Dunnett's Test Control (Placebo)
Placebo	88	19.5	0.066	0.005	—
Zaleplon 5 mg	86	15.5	—	0.366	0.116
Zaleplon 10 mg	90	12.5	—	—	0.010

TSO was also significantly shorter than placebo in the zaleplon 10 mg group but not the 5 mg group (median zal=17.5 minutes vs placebo 22.5 minutes p=0.002). This was a secondary efficacy variable and there was no correction for multiple secondary efficacy comparisons.

Conclusion

This study represents a positive study for the treatment indication of transient insomnia using the first-night-effect model. Given the small treatment and statistical difference in

the primary efficacy variable it is difficult to interpret the statistical significance of the TSO analysis without correction for multiple comparisons. The median difference in TSO was 5 minutes; this was a smaller treatment effect than the LPS median value yet with a smaller p-value.

7.2.6.2 Study 209-GE A Randomised, Double- Blind, Single- Dose, Placebo- and Zopiclone- Controlled, Four- Way Crossover, Polysomnographic Study of Zaleplon in a Four- Hour Phase Advance Manipulation of Sleep Onset

Investigators and sites
Investigators, and site at which subjects were studied was

B. Dietrich, MD (study site #20915)
L. A. B. GmBH & Co
Wegenerstrasse 13
89231 Neu- Ulm
Germany
n= 28

Objectives
The primary objective of this study was to compare the efficacy of 5 mg and 10 mg of zaleplon versus placebo, as measured by polysomnographic (PSG) recording, in a four-hour phase advance manipulation of sleep onset.

Study Population
Subjects in this study were healthy men and women, aged 18-45 years with normal and regular sleeping habits. There were 28 subjects.

Design
This was a single center, single dose, randomized, double blind, double dummy, placebo and zopiclone controlled, four way crossover study that was conducted at a single investigational site. A 4 day screening period was followed by four treatment periods, separated by 5 to 10 day washout intervals. The crossover design incorporated 7 Latin squares.

Each treatment period consisted of two nights. The first was a readaptation night, when subjects received single- blind placebo at their usual bedtime. On the second night, the subjects' bedtime was 4 hours earlier (phase advance), shortly after administration of double- blind study medication.

Assessments
Efficacy assessments were PSG recordings. Psychometric testing, neurologic exams, psychiatric screening, physical exams, urine pregnancy, and clinical laboratory tests, and ECGs.

Analysis Plan
The primary analysis was performed using an intent- to- treat (ITT) principle, that is, including those subjects who took at least one dose of randomized medication. The primary efficacy parameters were LPS and sleep efficiency during the first 4 hours recorded during the phase advance night (night 2) of treatment in periods 1, 2, 3 and 4.

For primary and secondary efficacy parameters, treatments were compared using analysis of covariance (ANCOVA) for the crossover design with subject, period and treatment as factors and the baseline value (night 1 in each period) as a covariate. The primary treatment comparisons of interest were zaleplon 5 mg and placebo and zaleplon 10 mg and placebo. Secondary treatment comparisons were zopiclone and placebo, zaleplon 5 mg and zopiclone, zaleplon 10 mg and zopiclone, and zaleplon 5 mg and zaleplon 10 mg. Pairwise treatment comparisons were made regardless of the outcome of the overall treatment comparison. For the primary treatment comparisons (zaleplon 5 mg versus placebo and zaleplon 10 mg versus placebo) Dunnett's test was used to adjust for multiple comparisons. Otherwise for secondary treatment comparisons, p- values are presented unadjusted.

Patient Disposition
Twenty- eight (28) subjects were randomly assigned to a treatment sequence of zaleplon 5 mg, zaleplon 10 mg, zopiclone 7.5 mg and placebo during the 4 periods of the study. All subjects completed all arms of the study and none dropped out.

Baseline Demographics/Severity of Illness
The mean age of the subjects was 31.6 years. Twelve were women and 16 were men. All were white (Caucasian) and all were healthy volunteers. There were no differences in treatment groups because of the crossover design and the fact that all subjects completed all of the treatment arms.

Concomitant Medications
Eleven of the twelve women were taking concomitant medicines. Nine took oral contraceptives and the remaining two women took antivirals (Aciclovir and Zorivax).

Efficacy Results

Though there were significant differences in sleep efficacy there was no difference in the LPS values in any of the active treatment groups compared to placebo.

Table 7.2.6.2.1 LPS (minutes) ITT population study 209-GE

				p-value difference from			
				Zaleplon		Zopiclone	
Night	Treatment	n	Median	5 mg	10 mg	7.5 mg	Dunnett's Test Control (Placebo)
Night 1	Placebo	28	14.87				
	Zal 5 mg	28	18.8				
	Zal 10 mg	28	13.8				
	Zop 7.5 mg	28	18.3				
Night 2	Placebo	28	16.3	0.33	0.94	0.50	
	Zal 5 mg	28	11.5		0.37	0.75	0.51
	Zal 10 mg	28	13.5			0.55	1.00
	Zop 7.5 mg	28	14.3				

Conclusion
This represents a failed study for the indication of transient insomnia using the model of phase advance manipulation.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of response

Age
Phase III studies of patients aged ≥ 65 years had significantly decreased TSO at 5 mg/day where the lowest effective dose in non-elderly patients was consistently 10 mg/day. Studies 301, 303, and 307 looked at non-elderly adults and had intermittent improvement in median TSO in the 5 mg groups where improvement in the 10 mg groups was almost uniformly consistent in studies 301, 303 and 307. Study 307 did not have a 5 mg group. Studies 306 and 308 focused on elderly adults and contained only 5 and 10 mg groups. TSO was uniformly shortened in all zaleplon dose groups tested. Given this response in the elderly, it appears that the

minimum effective dose in patients over age 65 would be 5 mg/day and in non-elderly adults (aged 18-65) the minimum effective dose would be 10 mg/day.

The sponsor explored this question by pooling some phase II sleep lab studies (203, 204, and 205) with the phase III studies reviewed above. They found a significant treatment by age interaction at week one and week two (p=0.025 and 0.017 respectively).

Other Potential Subgroup Interactions
The sponsor examined potential differences among men and women patients with respect to treatment response and found no differential response. No analyses were performed with respect to potential inter-ethnic differences.

7.3.2 Size of Treatment Effect
Median decreases in TSO in the phase III studies ranged from 8 to 20 minutes better for zaleplon 10 mg than placebo. All of these differences were statistically significant. These differences represent 16-33% less time to sleep onset respectively. These are mild to modest improvements at best yet they are comparable to active comparitors.

7.3.3 Choice of dose
Zaleplon 10 mg is the least effective dose in phase III studies of patients aged 18-65. Zaleplon 5 mg is the least effective dose in studies of patients aged 65 and older. Doses greater than 20 mg were not tested in the phase III trials in patients aged 18-65. Doses greater than 10 mg were not tested in phase III trials in patients aged 65 and older. Therefore the most rational dosing, based on the body of the available data, strongly suggests that zaleplon 10-20 mg at bedtime is effective at decreasing TSO in patients 18-65; however, patients who are older than 65 will receive effective reduction in TSO from 5 mg and should not exceed 10 mg at bedtime.

7.3.4 Duration of treatment
Controlled phase III trials extended to 28 days in patients aged 18-65. Zaleplon doses of 20 mg at bedtime were more consistently effective at reducing TSO in patients with chronic insomnia. There are only 14 day studies of patients aged 65 and older. The extension phase studies were useful for monitoring adverse events that might only appear rarely or with extended treatment; however, they were uncontrolled and offer little to suggest that there is any benefit to treatment extended beyond 28 days.

7.4 Conclusions regarding efficacy

The 5 phase III studies positively supported zaleplon as an effective treatment for chronic primary insomnia as measured by TSO. TTS and NAW were not consistently more effective than placebo. One study supports the use of zaleplon for the treatment of transient insomnia by the first-night-effect model. This reviewer does not agree with the sponsor's contention that study 209-GE provides support for the use of zaleplon in treating transient insomnia that most fits the model of phase shift manipulation (jet lag or shift work changes).

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The sponsor submitted a safety database that consisted of all patients exposed to zaleplon. The sponsor chose to pool the safety data based on design, location, and duration of studies for the purpose of descriptive presentation and statistical analyses. This pooling is appropriate and is discussed in section 5.1. The electronic submission did not included the raw safety data therefore the review was dependant upon the sponsor's compilation of the data into tables.

The sponsor provided case report forms (CRF) for all patients who died or dropped out of a study due to an adverse event. The sponsor provided narrative summaries for patient deaths, drop outs, serious adverse events, and potentially clinically significant laboratory values, ECGs, and vital signs.

Safety analyses of dropouts were based on placebo controlled studies of 5-28 days (group D [see section 5.1]) for statistical comparison, and descriptive data was given for patients who took zaleplon in the open label long term phases of protocols 302, 304, 306, 308, and 312 (group F [see section 5.1]).

To examine treatment emergent adverse events, the sponsor used the group C pool (28 day placebo controlled studies 204, 301, and 303) because of study design homogeneity and longer exposure to zaleplon.

Individual patients are identified by their patient numbers only. The patient numbers represent the protocol, study site, and individual patient (e.g. 30610-5236 represents study number 306, investigator 10, and patient 5236). Patients who went on to participate in the open label long term studies were assigned new patient numbers except in studies 306 and 308 where they retained their original patient number.

8.1.1 Deaths

There were two patient deaths during the development program of zaleplon.

One patient died during a clinical trial of zaleplon or within 1 month after treatment for any treatment group. Patient No. 11-207-2 in protocol L846/PE2/931007, a study done in Japan, was a 57-year old Asian man who participated with a diagnosis of primary insomnia. This patient had received 15 mg zaleplon daily

from 24 February 1994 through 28 February 1994 (a total of 5 days) when he dropped out of the study due to headache and palpitations. He then received zopiclone 15 mg daily from 1 March 1994 through 3 March 1994. He was seen on 03 March 1994 at which time the adverse events had resolved and he showed no evidence of depression. On post-study day 4 (4 March 1994) the patient committed suicide by hanging. The investigator judged this event unrelated to study drug administration.

The other patient death occurred before the start of double blind therapy. Patient 30850-0010, an 82-year old woman, died suddenly during the placebo run-in phase of study 308-EU, before any double-blind test medication had been given. The cause of death was unknown and the family did not want an autopsy performed.

8.1.2 Serious Adverse Events

The [redacted] medical monitor reviewed all study events to identify patients and subjects with serious study events. This identification was based on the regulatory definition of serious study events, which includes any adverse drug experience suggesting a significant hazard, contraindication, side effect, or precaution plus events that the sponsor wished to consider serious. Serious adverse drug experiences included those that are fatal or life- threatening, are permanently disabling, require inpatient hospitalization, or are congenital anomalies, cancer or overdoses. Additionally, while they may not be considered serious by the Agency criteria, pregnancy and certain CNS events of particular clinical interest, such as hallucinations, amnesia, ataxia, and depression, were considered by the sponsor as serious and discussed in the ISS.

Based on these criteria, the medical monitor determined that 107 patients and subjects treated with zaleplon in Phase II and III trials experienced serious study events (not including events that occurred during placebo run-out and poststudy periods; once a patient received one dose of placebo in the run out phase, a serious adverse event was not counted as part of the study). The list of serious study events was based solely on the medical monitor's judgment of the clinical seriousness of the event without regard to the probability that the study drug actually caused the event.

Table 8.1.2 in the appendix lists the patients and the adverse event considered serious in the Group G (all non-Japanese phase II/III patients). There were four patients who experienced an event that was considered serious. Only one of those events (patient L846/ME2/940426 12-215-2 discussed in section 8.1.2.2)

was judged by this reviewer as likely being related to zaleplon.

Most serious adverse events (SAE)reported in zaleplon treatment groups were in the nervous system and cardiovascular categories. The individual serious events reported most frequently in zaleplon-treated patients were surgical procedures (14 patients), hallucinations (12 patients on zaleplon and 1 during placebo run-out after zaleplon 5 mg), and accidental injury (12 patients). Surgical procedures were also the most frequently-reported serious event inpatients taking placebo; hallucinations were the most frequently-reported serious event among patients receiving comparator drugs.

8.1.2.1 Hallucinations

In Phase II/ III studies, hallucinations that were judged to be serious occurred in 16 patients, across all treatment groups, including zaleplon (12 patients), placebo (1), and comparator groups (3). All of these hallucinations were brief and resolved without sequelae; most did not lead to discontinuation from the study. The hallucinations that occurred with zaleplon- treatment were more common at higher doses. These experiences included illusions, hypnagogic hallucinations, and hallucinations. The patients with hallucinations that were considered serious are listed in Table 8.1.2.1 in the appendix.

The rate at which hallucinations were reported is roughly the same for both zaleplon and all comparitors even if one includes patient 30820-0004 (13/2831 [4.5×10^{-3}] zaleplon vs 3/560 [5.4×10^{-3}] all other comparitors. There were no reports of hallucinations on placebo except for patient 30820-0004 which was during the placebo run-out. The character and duration of the reported hallucinations were similar except for two cases, patients 30820-0004 and 30325-0271. The following are brief summaries of these cases.

30820-0004 This 70- year- old woman was randomly assigned to receive zaleplon 5 mg on 25 Jan 1996. Her medical history included hypertension, hypercholesterolemia and venous insufficiency, treated with propranolol, fenofibrate, flavonoid and spironolactone. She received zaleplon 10 mg in the open-label phase, and then experienced auditory hallucinations on 03 Aug 1996 in the single-blind placebo run-out phase of the open-label period. It was described as buzzing sounds while watching the TV. The investigator judged a possible relationship to study medication. The severity was judged moderate, and the duration was 12 days (until 15 Aug 1996, after the end of study). The hallucinations disappeared completely thereafter. These

hallucinations were probably not related to zaleplon.

30325-0271 This 42- year- old woman was randomly assigned to receive zaleplon 20 mg on 28 Oct 1994. The patient's medical history was unremarkable and no relevant findings were reported on physical examination. On 24 Oct 1994 (placebo run- in phase) the patient suffered from visual hallucinations of moderate severity. This event, which persisted, was assessed as being remotely study drug related. It consisted of seeing an object moving. It is not known how much time after drug intake this symptom appeared, but according to the investigator's comment, the hallucination may have been due to her fatigue. On 28 Oct 1994, study day 1, the patient suffered from memory impairment of moderate severity, which persisted, and was considered possibly related to study drug. On 11 Nov 1994, she complained of unreal feeling, noise sensitivity, light sensitivity, bad taste in mouth, depression, tremors. These events were moderate in severity. Others, which were severe, included muscle twitching, vertigo, and visual disturbances. All these symptoms were assessed as definitely not study drug related. On 17 Nov 1994, the patient withdrew from the study secondary to all events described above. To summarize, this patient experienced hallucinations along with multiple sensory symptoms before study drug was administered yet while receiving placebo. These hallucinations were unrelated to zaleplon.

Other reports of hallucinations with zaleplon and active comparitors followed a pattern. They were of shorter duration (3 minutes to 3 hours), closely followed drug administration, visual, and more commonly reported at higher doses.

A case that also lead to dropout, that was likely to be drug related, occurred with patient 30801-0033. This 76- year- old woman was randomly assigned to receive zaleplon 10 mg on 30 Oct 95. Her medical history included "psycho vegetative dysregulation" [sic] - symptomless for 3 years, and leg ulcer treated with a plant extract. On 2 Nov 95 at 23: 10 (the 4th study day), in the double- blind phase, the patient experienced visual, kinesthetic and tactile hallucinations for 3 hours, and then recovered without specific medication, to be withdrawn the next day. The investigator also considered this event probably related to the study drug.

Other CNS events(depression, amnesia, confusion) that the sponsor considered as serious accompanied hallucinations in two 21 year old women who incidently were taking the same oral contraceptive and were enrolled at the same investigation site.

20429-0014 This 21- year- old woman was randomly assigned to receive zaleplon 10 mg on 29 Sep 1994. Concomitant medication was Cilest, an oral contraceptive. The patient felt signs of moderate depression and experienced moderate tiredness, loneliness, and crying from 6 Oct through 26 Oct 1994. In addition on 18 Oct 1994, after taking the study drug at 10: 30 PM, she experienced severe visual hallucination, which included seeing things that did not exist. Her speech became disinhibited for about 20 to 30 minutes and she only partially remembered the episode the next morning. This patient had not had hallucinations before taking the study drug. No treatment was given. The hallucinations were considered to be drug related by the investigator. The patient completed the study on 28 Oct 1994 without any medical sequelae. She took the last dose of active treatment on 26 Oct 1994. The patient was blind to the placebo and her symptoms of depression were reported as present starting on the day zaleplon begin and lifted the day after it was stopped and the placebo washout began. The depression, confusion, amnesia, and hallucinations were all likely to be related to zaleplon.

20429-0013 This 21- year- old woman was randomly assigned to receive zaleplon 20 mg on 24 Sep 1994. Concomitant medication was Cilest, an oral contraceptive. On 26 Sep 1994 (study night 3), the patient reported hallucinations (specific descriptions were not present), illusions (changes in perspective), confusion, and felt "drunk- like". These symptoms began approximately 15 minutes after drug intake and she fell asleep after 30 minutes. She reported no recall of this in the morning. No treatment was given. In the opinion of the investigator, this study event was probably related to study drug. The patient did not experience hallucinations before taking the study drug. Additionally, the patient reported that she felt increasingly depressed and tired during the study period, which impaired her daily life and was "extremely unpleasant" (30-day duration). No specific treatment was provided. After she stopped taking the study drug on 21 Oct 1994 she felt much better. The patient completed the study on 23 Oct 1994. In the opinion of the investigator, this study event was probably related to the study drug, and was clinically significant.

Quite bizarre hallucinations were reported by patient 20110-1048. This 47- year- old woman was randomly assigned on 23 Jun 1992 to receive triazolam 0.25 mg/ day , zaleplon 40 mg/ day, placebo, and zaleplon 10 mg/ day according to a four- way crossover design. She completed double- blind treatment on 23 Jul 1992. On 21 Jul 1992, after receiving zaleplon 10 mg, the patient

reported hallucinations of moderate severity in which she saw "red and purple dots on the ceiling, the ceiling tiles coming together and running down the walls, and a big white bird on the ceiling". The hallucinations lasted 45 minutes and resolved without residual effects. No action was taken.

31230- 0002 This 24- year- old woman was assigned to receive open- label zaleplon 10 mg/ day on 16 Feb 1996 and titrated to 20 mg/ day on 23 Feb 1996. This patient had been randomly assigned to receive zaleplon 10 mg/ day in week 1 and 20 mg/ day in week 2 in the double- blind study (patient 30718- 0001) on 17 Jan 1996. The patient completed double- blind treatment on 30 Jan 1996. On 08 Aug 1996, open label study day 175, while taking zaleplon 20 mg/ day, approximately 20 minutes after taking study drug, the patient felt as if she were floating and that her bed had shrunk and was being carried by midgets. She spoke to the midgets, but they didn't talk back. She reported seeing the flashing green light on her VCR become a long ball of light that changed color (red to orange to yellow) and looked like a 3D snowflake that kept rotating. She stated she knew she was not dreaming and knew what she was seeing was not real. She does not know how long the episode lasted, but thinks she fell asleep shortly afterwards. The incident was classified as a mild hypnagogic perceptual alteration. The patient had experienced a previous benign perceptual alteration in 1994 after taking a sedative. The patient continued in the study, but at a decreased dose.

20209- 1125 This 60- year- old woman was randomly assigned on 23 Sep 1991 to receive placebo, triazolam 0.25, zaleplon 20 mg/ day, and zaleplon 60 mg/ day according to a four- way crossover design. On 29 Oct 1991, the first night of the fourth treatment period, after taking zaleplon 60 mg, the patient reported that she "thought my room was full of people". These symptoms allegedly lasted 2 hours, but she sought no medical help and fell asleep 3 hours after dosing. The following morning, she complained of headache and required Tylenol 650 mg. She recovered completely without sequelae.

Severe hallucinations of three minutes duration were reported by patient 30710-0007; however, the character of the hallucinations was not described in the profile and there was no CRF provided as the patient ostensibly dropped out to take employment.

Though the comparitor group hallucinations were of comparable frequency and duration there were no descriptions in two of the three cases. None of the reported hallucinations in the comparitor group dropped out while four patients dropped out of

the zaleplon studies due to hallucinations.

8.1.2.2 Amnesia

There were 10 cases of amnesia that the sponsor designated as serious. One patient received zaleplon 10 mg (30319- 0229); this patient completed the study. One (1) patient (20109- 1039) had received zaleplon 40 mg. Her amnesia resolved, and she completed the study. Two (2) patients (30105- 4336, 20420- 0038) had received zolpidem 10 mg. The remainder of cases occurred in patients receiving zaleplon 20 mg. Table 8.1.2.2 lists these cases.

Table 8.1.2.2 Patients reporting amnesia in phase II/III studies

Patient Number	Age (y)	Sex	Dose at Onset	Adverse Event	Investigator Assigned Drug Relationship
30319- 0229	35	M	Zaleplon 10 mg	Amnesia, thinking abnormal**	Possibly related
20430- 0071	30	F	Zaleplon 20 mg	Amnesia	Possibly related
30325- 0271	42	F	Zaleplon 20 mg	Hallucinations,** tremor, amnesia muscle twitching, vertigo, visual disturbances**	Not related
30715- 0005	52	M	Zaleplon 20 mg	Amnesia, depersonalization**	Possibly related
31218- 0006	26	F	Zaleplon 20 mg	Amnesia	Related
31233- 0005	44	F	Zaleplon 20 mg	Amnesia	Probably related
31228- 0003	46	F	Zaleplon 20 mg	Amnesia, ataxia, speech disorder	Probably related
20109- 1039	49	F	Zaleplon 40 mg	Amnesia	Probably related
20420- 0038	31	M	Zolpidem 10 mg	Amnesia	Possibly related
30105- 4336	48	F	Zolpidem 10 mg	Amnesia	Probably related

**Concomitant adverse events occurring with amnesia

Patient 30325-0271 was discussed in section 8.1.2.1 and these events were likely unrelated to zaleplon in her case.

Patient 30319-0229 complained of amnesia and abnormal mentation for the majority of this 28 day study. This 35- year- old man was randomly assigned to receive zaleplon 10 mg on 26 Dec 1994. On 28 Dec 1994 (study day 3), new symptoms appeared, including macular eruption, concentration difficulties, and tremor. The maculous eruption was of mild severity, persisted 34 days. The difficulties in concentrating was of moderate severity, and continued for 29 days. The tremor persisted for 10 days and was of mild severity. On 03 Jan 1995, the patient complained of moderate amnesia that continued for 21 days. The patient completed the study. These events are likely to be related to

zaleplon.

Patient 20430- 0071 complained of amnesia and visual disturbances. This 30- year- old woman, who had headaches in her medical history, was randomly assigned to receive zaleplon 20 mg on 12 Sep 1994. On 13 Sep 1994, she complained of mild visual disturbances of 20 minutes' duration. On 23 Sep 1994, while the patient was awake but with the lights off, she complained that things were moving and that objects were transformed into persons. The patient completed the study on 11 Oct 1994. On 17 Sep 1994, she complained of horizontal diplopia, drowsiness, difficulty in speaking, and word- finding difficulties. These symptoms occurred 15 minutes after she took the study drug (10:45 PM) and more than 8 hours after she had drunk a glass of champagne (the patient admitted to rarely drinking alcohol). She phoned her mother, but the next day, she did not remember this. Findings of a neurological exam on 19 Sep 1994 were normal. These events are likely to be related to study drug.

Patient 30715- 0005 experienced fatigue, asthenia, and amnesia. This 52 year- old man was randomly assigned to receive zaleplon 10 mg/ day on 07 Nov 1995 and titrated to zaleplon 20 mg/day on 14 Nov 1995. On 13 Nov 1995, study day 7, the patient experienced worsening fatigue. On 22 Nov 1995, study day 16, while on zaleplon 20 mg/ day he experienced severe loss of memory and a severe unreal feeling noted. On 26 Nov 1995, study day 20, the patient took the last dose of study drug. He withdrew from the study because of fatigue. The patient's condition improved after discontinuation of the study drug. These events are likely to be related to zaleplon.

Patient 31218- 0006 experienced one episode of amnesia over a long treatment period that did not recur. This 27- year- old woman was assigned to receive open- label zaleplon 10 mg/ day on 17 May 1996 and titrated to 20 mg/ day on 13 Jun 1996. This patient had been randomly assigned to receive placebo in the double- blind study (patient 30704- 0011) on 19 Apr 1996, and completed double- blind treatment on 02 May 1996. On 08 Jul 1996, open label study day 53, while on zaleplon 20 mg/ day, anterograde amnesia was reported . The event did not reoccur. The patient continued in the study. This type of event occurs with sedative hypnotics in general and is also likely to be related to zaleplon; however, it is difficult to determine causality with this particular isolated event.

Patient 31233- 0005 discontinued the study after one episode of moderate memory impairment while taking zaleplon 20 mg/day.

There was one patient in the Japanese studies who experienced amnesia (L846/ ME2/ 940426 12- 215- 2). This 47- year- old woman experienced unconsciousness and amnesia ("blackout") after combining alcohol with zaleplon and etizolam.

The rate at which amnesia was reported for zaleplon [7/2831 (0.25%)] was comparable to zolpidem [2/560 (0.35%)] both of which were greater than placebo [1/1028 (0.097%)]. All cases were judged by this reviewer as likely to be related to either zaleplon or zolpidem. None of the cases would have met the Agency criteria as serious adverse events.

8.1.2.3 Other CNS serious adverse events likely to be related with zaleplon

Dizziness
There were three reported cases of dizziness one of which was associated with a fall (30105- 4071). This was a 39 year old male who was randomized to zaleplon 20 mg. After taking the study drug he did not go to bed as instructed but remained up. He became dizzy and fell injuring his mildly right knee. The patient was observed to take the study drug on a subsequent night and not go to bed whereupon he became dizzy again. The investigator dropped him from the study due to his noncompliance around this issue. The other two (20515-0026 and 20520-0042) were mild and self limited. All were likely to be associated with study drug. There was one case of ataxia, vertigo, and dizziness associated with zolpidem 10 mg (30309-0475) where the patient fell but sustained no injury. This patient dropped out of the study for this adverse event. None of these events would have met Agency threshold for "serious."

Depression
In addition to the patient who committed suicide (Patient No. 11-207-2 in protocol L846/PE2/931007 discussed in section 8.1.1) there were three reported cases of depression- 20429-0013 (discussed in section 8.1.2.1), 20429-0011, and 30419-0529. The suicide patient was taking zolpidem for three days at the time of the suicide and had discontinued zaleplon 4 days earlier due to lack of efficacy. Even though the Japanese study included more severely depressed patients that the other phase II/III studies, this patient was diagnosed on the CRF as a primary insomnia patient. The fact that the patient was taking zolpidem at the time of the suicide is a confounding factor and no causal relationship to zaleplon can be drawn.

The other three cases were likely to be related to zaleplon;

however, they were mild. Patient 30419-0529 dropped out due to depression and lack of efficacy. It is impossible to ascertain which reason was truly the primary cause of the dropout. Patient 20429-0011 remained in the study and was depressed for the duration of drug treatment (much like patient 20429-0013) and received supportive psychotherapy. Patient 20429- 0014 described in section 8.1.2.1 reported crying spells and loneliness but was not coded as reporting depression even though the summary reports moderate depression. These three cases had no history of depression prior to the study, reported depressive symptoms during the double blind treatment phase, and symptoms abated during the placebo washout period. This leads to the conclusion that these symptoms were likely related to zaleplon. There were no cases of depression reported in the placebo or comparator groups.

Hostility
There was one case of hostility reported in the zaleplon group (patient 30348- 0061). This 53- year- old man was randomly assigned to receive zaleplon 10 mg on 18 Aug 94. On 28 Aug 94 at 8:00 am, the patient had feelings of aggression and irritability. The severity was assessed as being moderate. The investigator reported that the patient could not sleep and that he was experiencing problems at work. The patient withdrew consent on 01 Sep 1994 secondary to hostility and nervousness. There was no report of acting out aggressively.

There was also one patient in the placebo group with a report of hostility (patient 30708- 0005). It described the patient as noting severe internal aggressiveness and having expressed aggressive thoughts.

Thus 1/2831 (0.04%) is the proportions of zaleplon patients reporting hostility and 1/560 (0.2%) is the proportion of placebo patients reporting hostility.

8.1.2.4 Syncope
Five patients reported syncope. Four of these patients were enrolled in zaleplon groups and 1 was enrolled in the placebo group.

Two of the zaleplon patients were described as having a vasovagal reflex reaction following blood drawing. Patient 30608- 5287 was a 76- year- old man who was assigned to receive 5 mg of zaleplon. On study day 14, the patient lost consciousness while having blood drawn in the investigator's office. The second patient (20209- 2140) was a 29- year- old man assigned to 60 mg of

zaleplon who also experienced an episode of syncope while blood was being drawn on study day 8, before taking the drug.

Two other zaleplon patients were reported to have had syncopal episode that were not related to blood drawing. Patient 30716-0054, a 22- year- old woman was assigned 10 mg of zaleplon. She had a history of syncope. Patient 31227- 0009 was taking 20 mg of zaleplon when she reported on study day 47 intermittent fainting spells. The patient's laboratory values and vital signs revealed no significant abnormalities throughout the study.

Patient 30628- 5178, a 66- year- old man, was assigned to the placebo group. He had a history of heart disease. On study day 6, he experienced a syncopal episode and lost consciousness. The proportions of patients reporting syncope are roughly equal between placebo [(1/560) 0.2%] and zaleplon [(4/2831) 0.1%]. One of the cases (patient 31227- 0009) of syncope is possibly related to zaleplon. The others are unlikely related to zaleplon.

8.1.2.5 Chest Pain/Angina

Eight patients taking zaleplon, two placebo patients and one zolpidem patient were reported to have experienced chest pain or angina. The proportions of patients reporting syncope are roughly equal between placebo [(2/560) 0.4%] and zaleplon [(8/2831) 0.3%]. Patients who reported chest pain are listed in table 8.1.2.5 in the appendix.

Patient 30628- 5176 experienced chest pain, palpitations, and ECG changes. This 73- year- old woman was assigned to receive open-label zaleplon 5 mg/ day on 30 Aug 1995. This patient had been randomly assigned to receive zaleplon 10 mg/ day on 09 Aug 1995 and completed double- blind treatment on 23 Aug 1995. Her medical history was significant for hypertension, asthma, hypothyroidism, and a hysterectomy for fibroids. On 05 Mar 1996, open label study day 188, she reported heart palpitations and left- sided chest heaviness. These recurred on 07 Mar 1996. She was hospitalized for evaluation. Serial ECGs and CPKs levels showed no evidence of myocardial infarction. However, premature atrial complexes and premature ventricular complexes were noted. These ECG changes were not seen later. A stress test revealed no ischemia, but the patient experienced an asthma attack that resolved quickly. Discharge diagnoses were asthma and hypertension. on 08 Mar 1996 she was discharged in stable condition on Dyazide, Synthroid, Cardizem, Premarin, Levoxyl, in addition to Azmacort, Serevent, and albuterol inhalers. The patient continued in the study. This event was unlikely to be related to zaleplon.

Patient 30838- 0121 only took one dose of zaleplon but reported chest pain, back pain, and foot edema of 10 days duration. The ECG and laboratory studies were negative for any sign of myocardial infarction and the patient was hospitalized.

Patient 30610- 5080 experienced abnormally high BUN along with chest pain. This 68- year- old man was assigned to receive open-label zaleplon 5 mg/ day on 18 Jul 1995. This patient had been randomly assigned to receive zaleplon 5 mg/ day on 27 Jun 1995 and completed double- blind treatment on 11 Jul 1995. This same day, study day 14, the patient's BUN was 36 mg % (normal 4.0-24.0 mg %), compared to screening values of 31.0 mg % and 33.0 mg %. The creatinine was 2.0 mg % (normal 0.8- 1.6 mg %), compared to screening values of 1.9 mg % and 2.0 mg %. On 13 Oct 1995, open label study day 88, while taking zaleplon 10 mg/ day, he was hospitalized for observation because of chest pain and shortness of breath. He was released from the hospital with the diagnosis of stress- related chest pain. During hospitalization, he missed 2 doses of zaleplon, but continued in the study. It is unlikely that these events were related to zaleplon. The creatinine and BUN were elevated significantly before the beginning of the study. The increase with subsequent return to baseline values during the study appeared to be this patient's random fluctuation in elevated BUN and creatinine which probably represents chronic renal failure predating the commencement of the study.

Patient 30610- 5326 This 72- year- old woman was assigned to receive open- label zaleplon 5 mg/ day on 23 Feb 1996. This patient had been randomly assigned to receive zaleplon 5 mg/ day on 02 Feb 1996, and completed double- blind treatment on 15 Feb 1996. A prestudy ECG on 19 Jan 1996 was interpreted within normal limits. An ECG on 22 Feb 1996 revealed ST depression, nonspecific ST- T abnormality, negative T in I, II, AVL, V3 through V6, and possible lateral ischemia. The patient did report symptoms of angina. Note that the patient was not taking zaleplon for 7 days when this report of angina and ECG was taken. The patient began open label zaleplon nonetheless. A poststudy ECG on 06 Jun 1996 revealed premature atrial contractions and was interpreted as normal. On 09 May 1996, open label study day 77, while taking zaleplon 10 mg/ day the patient fell in the bathtub. X- rays revealed no fractures and the patient was given hydrocodone, Darvon- N, and ibuprofen for pain. On 09 May 1996, the patient was withdrawn from the study because of the continued need for analgesics. It is quite possible that this patients accidental fall is related to zaleplon. Young healthy patients

have fallen shortly after taking zaleplon, but there was no mention of the temporal proximity of the fall and taking the drug. It is unlikely that the chest pain and ECG changes were related to zaleplon as the patient had been drug free for one week when these events occurred and after resuming the drug these cardiac events did not recur.

Patient 30709- 0003 experienced chest pain that was not characteristic of cardiac pain. This 39- year- old woman was randomly assigned to receive zaleplon 10mg/ day on 01 Apr 1996 and titrated to zaleplon 20 mg/ day on 09 Apr 1996. On 12 Apr 1996, study day 12, while on zaleplon 20 mg/ day the patient awoke with severe sharp pressure pain in her chest. The pain radiated to the back and right shoulder. The patient also developed a severe headache. The chest pain lasted for approximately 1 hour. She did not complain of shortness of breath or pleuritic pain. Changes in body position did not alter the pain. The patient reported mild parasternal tenderness the next morning, which lasted for approximately 48 hours. The patient did not take study drug from 12 to 14 Apr 1996. She completed the study on 22 Apr 1996. The pain is more characteristic of cholecystitis or pancreatitis (pain boring through to the back); however, there was no mention of clinical lab studies ordered and no lab values were listed as being potentially clinically significant. After re-challenge, the patient did not have a recurrence of symptoms. Though the investigator felt that this event was related to the drug, the lack of recurrence on re-challenge argues against this conclusion.

Other zaleplon patients reporting chest pain did not have ECG changes, the chest pain was not characteristic of cardiac pain, and their symptoms were self limited.

In summary, the cases of chest pain/angina described above were unlikely to be related to drug induced cardiac abnormalities. The accidental fall and dyspepsia may however be drug related.

8.1.2.6 Arrhythmias

There was only one arrhythmia that was likely to be drug related. This conclusion was made due to the normal ECG before the protocol began, the appearance of the arrhythmia during the study and its failure to spontaneously resolve during the study. This patient (30825- 0341) was an 87- year- old woman and was randomly assigned on 14 Dec 1995 to receive zaleplon 5 mg. The ECG at screening was normal. The patient then developed incomplete left bundle branch block and ventricular tachycardia. The AE

appeared on 10 Jan 1996, while taking zaleplon 5 mg in the open-label phase, and was not associated with any clinical symptoms. Another ECG was done on 15 Jan (day of withdrawal) and the abnormality was still present. She was not using any concomitant medication before or after this event. She was withdrawn from the study and there was no rechallenge. There was no post-study ECG; therefore it is unknown what the effect was of stopping the drug. The patient was quite elderly and mild arrhythmias are frequent at this age. Due to the temporal onset of the arrhythmia and its endurance throughout the study, this reviewer judged that this event may likely have been related to zaleplon. The subject of arrhythmias shall be discussed in section 8.1.8.

8.1.2.7 Overdoses

There were two zaleplon overdoses during the clinical development program. The 2½- year old son of patient 31230- 0010 unintentionally ingested between 2 and 4 zaleplon 10- mg capsules that had been dispensed to the patient, a total dose of 20 to 40 mg of zaleplon. The child was using Proventil and Vancenase inhalers and was taking cyproheptadine. He appeared "groggy" and was taken to a local emergency room, where he was given activated charcoal and IV fluids and observed. His symptoms resolved without sequelae.

Patient 22- 402- 2 (study L846/ PL2D/ 941207) was a 20- year old Asian man participating in a zaleplon study in Japan. He was assigned to the zaleplon 20 mg dosage group. He intentionally took an overdose of 100 mg of zaleplon along with 2.25 mg of triazolam. The patient appeared in a "daze" after this overdose, and vomiting was induced after 4 hours. His symptoms resolved without sequelae.

8.1.2.8 Other cardiac related serious adverse events

This 71- year- old woman was randomly assigned to receive zaleplon 2 mg/ day, zaleplon 10 mg/ day, placebo, and zaleplon 5 mg/ day, according to cross- over design on 07 Nov 1994, and she completed double- blind treatment on 06 Dec 1994. On 09 Nov 1994, study day 2, after receiving zaleplon 2 mg the patient developed an 8- beat, 4- second run of ventricular tachycardia. The subject was asymptomatic. She had a history of low blood pressure, and the screening ECG of 19 Oct 1994 revealed marked sinus arrhythmia with non- specific ST- T wave changes. On 29 Nov 1994, study day 22, after receiving placebo in period 3, she developed a 35- second run of atrial tachycardia. No action was taken and it was resolved without sequelae. At follow- up on 13 Dec 1994, the subject's ECG showed occasional supraventricular

premature complexes as well as the ST- T wave changes previously described. This patient clearly had pre-existing conduction abnormalities yet one can not rule out the possibility that zaleplon may have contributed to the short run of ventricular tachycardia. The other above described arrhythmias were unlikely to be related to zaleplon.

8.1.3 Drop outs and other Significant Adverse Events

8.1.3.1 Overall profile of dropouts
Table 8.1.3.1.1 in the appendix compares the drop out rates for each dose level of zaleplon and all zaleplon dose levels versus placebo and all comparitors (zolpidem, triazolam)in the group D pool. The drop out rate for group D zaleplon patients for adverse events was 53/2069 (2.6%) and for placebo it was 15/744 (2.0%). There was no statistical difference between the drop out rates for placebo and zaleplon. The active comparitor adverse drop out rate was 16/413 (3.9%). There was no relationship with dose and drop out rate in zaleplon treated patients.

The drop out rate was higher in the extended versus shorter term use. Of 1088 patients who enrolled in one of the open label, extended treatment studies (group F) 482/1088 (44%) dropped out for any reason and 94/1088 (9%) dropped out due to an adverse event. Table 8.1.3.1.2 in the appendix classifies drop outs in group F.

8.1.3.2 Adverse events associated with drop out
In group D, there were no adverse events leading to drop out that were statistically greater than placebo. There were no adverse events that accounted for a drop out rate of greater than 9/2069 (0.4%); this event was somnolence where the placebo rate was 1/744 (0.1%). Somnolence also represented the greatest difference between zaleplon and placebo in drop out rate; all other zaleplon drop out rates were lower and less different than placebo. The highest drop out rates were due to CNS related adverse events. The most frequent reasons for drop out in group D are listed in table 8.1.3.2.1.

Table 8.1.3.2.1 Most common reasons for drop out in group D			
Adverse event listed as reason for drop out	**All Zaleplon doses (≤ 20 mg) n=2069**	**Placebo n=744**	**p-value [Fisher's Exact test (two-tail)]**
Somnolence	9	1	0.47
Headache	8	3	1.00
Dizziness	6	2	1.00
Depression	6	2	1.00
Nervousness	6	1	0.68
Rash	5	1	1.00
Vertigo	4	0	0.58

Patients were allowed to take zaleplon for up to one year in group F. In group F the 9% dropped out due to adverse events over the open label exposure time. The most common adverse events leading to drop out in this pool of patients are listed in table 8.1.3.2.2.

Table 8.1.3.2.2 Most common adverse events leading to drop out in group F (long term, uncontrolled, open label, extension studies.	
Adverse Event	**Zaleplon patients n=1088**
Dizziness	16
Headache	14
Somnolence	14
Depression	9
Nervousness	8
Anxiety	6
Asthenia	6
Abdominal Pain	5
Accidental Injury	4
Thinking Abnormal	4

This review of adverse events leading to drop out in the long term treatment pool revealed the same pattern of events that occurred in the zaleplon treated patients in the pool of short term placebo controlled studies (group D).

8.1.4 Other search strategies

Benzodiazepines and benzodiazepine- like drugs have been associated with hyperexcitability phenomena such as daytime anxiety and early morning awakenings during treatment and rebound insomnia, anxiety and seizures after withdrawal. The sponsor set out to monitor the adverse events during the development of zaleplon.

8.1.4.1 Withdrawal emergent anxiety

In addition to the collection of treatment- emergent adverse events, specific instruments were used in several protocols to assess the possible occurrence of daytime anxiety and anxiety associated with the withdrawal of treatment. The State/ Trait Anxiety Index (STAI) was used in zaleplon protocol 203- US and the Zung Self- Rating Anxiety Scale (Zung- A) was used in protocol 204- EU.

Study 203 consisted of 14 days of double-blind treatment with either zaleplon 5 mg, 10 mg, placebo, or triazolam 0.25 mg in an elderly population. There were approximately 30 patients per treatment group. In study 203 there were no significant differences in STAI scores between zaleplon and placebo or triazolam treated patients. Daytime anxiety scores in each group were all numerically less at all time points during treatment and during the withdrawal period than at baseline.

Study 204 consisted of 28 days of double-blind treatment with either zaleplon 10 mg, 20 mg, zolpidem 10 mg, or placebo in a non-elderly population. There were approximately 30 patients per treatment group. The total scores for the Zung Anxiety (24-hour) Rating Scale were not significantly different between the various treatment groups at days 1 and 2 after withdrawal. All treatment and post treatment Zung Anxiety Scale scores were numerically less than at baseline.

The incidence of anxiety as a spontaneously reported adverse event in group D zaleplon patients [24/2069 (1%)] was comparable to placebo [11/744 (1%)]. The incidence of spontaneously reported anxiety in the group D comparitors patients was 17/413 (4%) which was statistically different than zaleplon ($p<0.001$, Fisher's Exact Test).

This reviewer concludes that anxiety during treatment or after discontinuation is unlikely to be a drug related event.

8.1.4.2 Rebound insomnia

Rebound insomnia was operationally defined as a temporary worsening from baseline values of symptoms of insomnia once therapy was discontinued. The effects of discontinued zaleplon therapy on rebound insomnia were evaluated by using sleep questionnaire measures of TSO, TTS, and NAW and by PSG measures of LPS, TST, and NAASO. Patients were considered to have experienced rebound insomnia if their placebo run out night +1 sleep scores exceeded their worst baseline sleep score. This was a very conservative measure of rebound insomnia; the baseline sleep score values were averaged over one week in the efficacy analysis. Fisher's Exact Test was employed to test group difference in the incidence of rebound insomnia. The result of the Fisher Exact Test for TSO and TSS follow in table 8.1.4.2.1.

Table 8.1.4.2.1 Incidence of rebound insomnia on night +1

		Zaleplon			Triazolam	Zolpidem	
Treatment Duration **TSO**	Protocol #	5 mg	10 mg	20 mg	0.25 mg	5 mg	10 mg
2- week Studies							
Nonelderly patients	203- US	ns	ns	-	0.04	-	-
	307- US/ CA	-	0.03	0.004	-	-	-
Elderly patients	306- US	ns	ns	-	-	0.04	-
	308- EU	ns	ns		---		-
4- week Studies							
Nonelderly patients	204- EU	-	ns	ns	-	-	ns
	301- US	ns	ns	ns	-	-	<0.001
	303- EU/ CA	ns	ns	ns	-	-	0.02
TSS							
2-week Studies							
Nonelderly patients	203- US	ns	ns	-	ns	-	-
	307- US/ CA	-	0.038	0.003	-	-	-
Elderly patients	306- US	ns	ns	-	-	<0.001	-
	308- EU	ns	0.028		---		-
4- week Studies							
Nonelderly patients	204- EU	-	ns	ns	-	-	ns
	301- US	ns	ns	ns	-	-	<0.001
	303- EU/ CA	ns	ns	ns	-	-	ns

The median difference in TSO after two weeks of treatment in non-elderly patients (studies 203 and 307) after withdrawal on night

+1 was 10 minutes greater in the zaleplon 5 mg group, and 15 minutes greater in the 10 and 15 mg zaleplon groups when compared to placebo. The active comparitor, triazolam 0.25 mg was 30 minutes longer than placebo. On night +2 the zaleplon 20 mg group median TSO was 5 minutes longer than placebo while the zaleplon 5, 10 mg group and triazolam 0.25 mg were 10 minutes less than placebo.

Elderly patients taking zaleplon did not differ from placebo patients in median TSO while active comparitor, zolpidem 5 mg, was 15 minutes greater on night +1. On night +2 there were no treatment groups with longer median TSO than placebo.

Differences in TSS and NAW were proportionally smaller and like the differences in TSO had disappeared by night +2. Differences in TSO, TSS, and NAW after 4 weeks of treatment followed similar patterns; however, the differences between treatment and placebo groups in rebound insomnia parameters were less than in the two week treatment groups. Thus, mild rebound insomnia after treatment with zaleplon does occur in all age groups and, on visual inspection, it appears to be dose dependent. Rebound insomnia appears to substantially if not completely resolve by the second night after discontinuation.

8.1.4.3 Withdrawal effects

Pharmacological dependence is a phenomenon that has been associated with chronic sedative-hypnotic use. Pharmacological dependence is defined largely by the appearance of certain symptoms when treatment is terminated. Among the symptoms commonly reported during this withdrawal period are panic and anxiety, perceptual disturbances, loss of appetite and weight loss, depressed mood, and, much less commonly, seizures.

The sponsor employed the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) in several double blind, placebo controlled, zaleplon studies (203, 204, 301, 303, and 307). During the study, patients were administered the BWSQ during the single blind placebo run-in, treatment, and withdrawal phases. The BWSQ was called a "Symptom Check List" (SCL). Withdrawal was defined as the emergence of three or more new symptoms after discontinuation. BWSQ values were collected during the first two days after discontinuation (days +1 and +2).

Results from the integrated analysis of the BWSQ data for zaleplon studies 203- US, 204- EU, 301- US and 303- EU/ CA are shown in Table 8.1.4.3.1. Patients with insomnia who were treated with 5, 10, or 20 mg of zaleplon for 2 weeks (203- US) or

4 weeks (204- EU, 301- US, and 303- EU/ CA) developed 3 or more new symptoms during the placebo run- out phase at a rate comparable to that for placebo- treated patients. Patients treated with zolpidem developed new symptoms at twice the rate of those treated with either placebo or zaleplon. This difference in the rate of emergence of withdrawal symptoms does not mean that zaleplon is safer than zolpidem with regard to withdrawal. It does, however, imply that the BWSQ is sensitive enough to detect differences between placebo and active treatment.

TABLE 8.1.4.3.1 BENZODIAZEPINE WITHDRAWAL SYMPTOM QUESTIONNAIRE:
PATIENTS WITH 3 OR MORE NEW SYMPTOMS DURING PLACEBO RUN-OUT

	Withdrawal Day 1	Withdrawal Day 2
Therapy Group	n (%)	n (%)
Placebo	13 (5.0)	14 (5.3)
Zaleplon 5 mg	12 (5.2)	13 (5.7)
Zaleplon 10 mg	14 (5.6)	15 (6.1)
Zaleplon 20 mg	14 (6.4)	12 (5.5)
Zolpidem 10 mg	28 (13.5)*	21 (10.2)
Triazolam 0.25 mg	1 (3.2)	0 (0)
* Denotes $p < 0.05$ vs placebo, Fisher's Exact Test.		

The sponsor also monitored withdrawal emergent adverse events (defined as adverse events previously unreported or adverse events that increased in severity after discontinuation of treatment). Adverse events that occurred 1% or greater in group D are listed in table 8.1.4.3.2 in the appendix.

There were no dose related increases in withdrawal emergent events. The most common withdrawal emergent adverse event was headache (zaleplon 5%); however, headache occurred at a comparable rate in the placebo group (4%). Abrupt withdrawal of zaleplon at doses ranging from 5-20 mg/day did not lead to tremulousness or seizures. Hallucinations were reported in a few cases while on drug but the rate at which hallucinations were reported decreased with discontinuation. Patients who experienced drug related hallucinations did so shortly after taking the drug (see section 8.1.2.1). Mean systolic blood pressure and pulse at the end of week 4 were not clinically significantly different from the post treatment phase. Depression as an adverse event occurred in a few cases but cleared with discontinuation as opposed to becoming worse (see section 8.1.2.3). There was no evidence for drug withdrawal related anxiety; however, rebound insomnia (which one may

consider a withdrawal symptom) was present and most likely drug related. All in all the strongest evidence for withdrawal and physiologic dependence is short duration post treatment rebound insomnia. This would therefore represent a very mild withdrawal.

8.1.5 Common adverse events

8.1.5.1 Approach to eliciting adverse events in the development program

A study event was defined as any negative event that a patient experienced during a study. This could be an adverse experience, a treatment- emergent sign or symptom, a new intercurrent illness, or a clinically important abnormal laboratory, vital sign, or ECG finding. The term "study event," which is used by W-AR, is synonymous with the term "adverse event," which is used by the FDA.

All study events, either observed by the investigator or one of his or her professional collaborators, or reported by the patient spontaneously or in response to a direct question (including self- ratings in questionnaires), were to be noted in the study events section of the patient's CRF. If any study event occurred after administration of the study medication, the patient was to be followed up with the appropriate treatment and close medical supervision. The investigator was to record the study event on the CRF and provide the date of onset, severity, relationship to study medication, duration (or the fact that it was still continuing), action taken, and outcome of the study event. A causality assessment was to be made for every study event by the investigator.

A treatment- emergent study event (TESE) category was defined to identify new events that may have been related to the administration of the study drug. TESE were defined as new study events, that is, events that started after the first dose of double- blind or active medication or, if the date of onset preceded the start of therapy, events that worsened during therapy. Also, an event that occurred during a placebo run- in or medication- free prestudy period and stopped before the initial dose of active or blinded study medication, but later recurred during the treatment period was considered a TESE. When it was not clear whether an event was treatment- emergent because of an incomplete or a missing start date, it was considered treatment- emergent.

8.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor employed the COSTART system of classifying verbatim adverse event terms. The glossary was reviewed and it was found that the verbatim terms were appropriately classified.

8.1.5.3 Selecting the best adverse event tables for categorizing adverse events

Group C is the most appropriate pool of patients from which to construct a 1% adverse event table for labeling. Group C comprises the double blind, parallel, placebo controlled, 28-day studies (see section 5.1). The 28 day pool was chosen as this represents the longest study period that is placebo controlled. The 14 day studies were excluded from this table so that emergent events that might only occur with longer treatment would not potentially be minimized by large numbers of patients who took the drug for shorter amounts of time. This table may be found in the appendix as table 8.1.5.3.1.

8.1.5.4 Identifying common and drug related adverse events

The usual criteria that the Division has employed as a definition for "common and drug related" is that an event occur at least 5% of the time (common) and at least at twice the rate of that of placebo (drug related). By this criteria, there were no events that were considered common and drug related.

8.1.5.5 Additional analyses and explorations

8.1.5.5.1 Dose dependence of adverse events

The sponsor stated that they examined all of the phase II/III data to determine if there were changes in frequencies of various adverse events that were a function of zaleplon dose. As with the 1% adverse event table, it is most appropriate to examine the 28 day, fixed dose, double blind, placebo controlled, parallel group, study pool (group C). Table 8.1.5.5.1 outlines the adverse events that demonstrated statistical significance by trend analysis.