Table 8.1.5.5.1 Adverse events reported at a rate of ≥1% of all patients in group C for which a significant dose-related trend was observed				
	Zaleplon			
Adverse Event	5 mg (n = 239)	10 mg (n = 274)	20 mg (n = 273)	p-value Linear Trend
Body As A Whole				
Headache	65 (27.2)	77 (28.1)	105 (38.5)	0.002
Digestive System				
Constipation	4 (1.7)	3 (1.1)	0 (0.0)	0.039
Nervous System	55 (23.0)	76 (27.7)	86 (31.5)	0.038
Amnesia	4 (1.7)	6 (2.2)	12 (4.4)	0.047
Hypesthesia	0 (0.0)	1 (0.4)	5 (1.8)	0.011
Skin And Appendages				
Herpes simplex	1 (0.4)	2 (0.7)	6 (2.2)	0.043
Special Senses				
Eye disorder	4 (1.7)	1 (0.4)	0 (0.0)	0.031

Herpes simplex is unlikely to be drug related and has tested as significant by chance. Eye disorder is a vague and uninformative category. The remaining correlations are somewhat expected with hypnotics. Though headache was the most commonly reported adverse event with patients taking zaleplon, it failed to meet criteria for common and drug related by the test in section 8.1.5.4. Nonetheless, the dose related incidence of headache is evidence that headache is likely to be a drug related adverse event. Amnesia is likely to be drug related as this is an adverse event that is associated with both benzodiazepine and non-benzodiazepine hypnotics.

8.1.5.5.2 Drug-demographic interactions

The sponsor performed analyses of the incidence of adverse events as a function age and sex. They stated that the number of patients from diverse ethnic backgrounds was not high enough to perform an adequately powered analysis of drug-ethnicity interactions.

Drug age interactions are difficult to interpret because patients over the age of 65 years never received more than 10 mg/day while patients age 18-65 years received up to 20 mg/day. Abdominal pain and tremor occurred more often in the 18-65 year old group as compared to the > 65 year old group. Though these were significant by Breslow-Day testing, the groups were exposed to radically different doses. Younger patients are most likely not more at risk for tremor or abdominal pain. One might be able to suggest that these adverse events are dose related; however, they failed to show dose relatedness in trend analysis.

Men and women received similar doses and analysis of differences in the reporting of adverse events is a valid comparison. Hallucinations were reported more commonly in women than men. Abnormal thinking was reported more often in men than women (see table 8.1.5.5.2.1). Breast pain is reported more often in women in the zaleplon group; however, this is more often a complaint in women than men in the general population. Facial edema was also identified as a sex-drug related interaction; however, this is probably due to multiple comparisons and represents a type I error.

Table 8.1.5.5.2.1 Analysis of relative risks by sex in group D pooled patients. Only adverse events which showed a statistical significance are displayed.

	Men				Women				
Body System	Zaleplon	Placebo	Relative		Zaleplon	Placebo	Relative		Breslow
Study Event	(n = 805)	(n = 293)	Risk	95% CI	(n = 1264)	(n = 451)	Risk	95% CI	p- value a
Body As A Whole									
Face edema	0 (0)	1 (< 1)	--	--	8 (< 1)	1 (< 1)	2.85	0.36-22.76	0.04
Nervous System									
Hallucinations	1 (< 1)	1 (< 1)	0.36	0.02-5.80	10 (< 1)	0 (0)	--	--	0.02
Thinking abnormal	11 (1)	0 (0)	--	--	10 (< 1)	5 (1)	0.71	0.25-2.08	0.03
Urogenital System									
Breast pain	0 (0)	1 (< 1)	--	--	5 (< 1)	0 (0)	--	--	0.01

a: Breslow p- value from Breslow-Day comparison of odds ratios of men vs women for a given adverse event.

8.1.6 Laboratory Findings

8.1.6.1 Extent of laboratory testing in the clinical development program

The sponsor performed clinical laboratory tests (CLT) on all patients participating in phase two and three studies. Generally CLTs were performed at screening, at baseline (one week before the administration of double blind treatment), the morning after the last dose of double blind treatment, and at follow-up (8-12 days after the end of double blind treatment). In study 307 there was no end of double blind treatment CLT performed. Studies 203, 204, and 205 provided for CLTs after the first day of double blind treatment; however, these protocols did not measure CLTs the day after the last dose but did so two days after the last dose.

The group D pool of patients consisting of 2069 patient who received zaleplon had baseline and follow-up CLTs performed on between 754 and 2006 of those patients depending on the specific CLT being performed. Likewise in that same pool, of the 744 patients who received placebo, between 146 and 716 had baseline and at least one follow-up CLTs performed depending on the CLT. Table 8.1.6.3.2.2 in the appendix reflects the total number of patients upon whom CLTs were performed by individual test along with the number of those patients who met criteria for potentially clinically significant(PCS)laboratory values.

A listing of the CLTs that were performed may be found in table 8.1.6.3.2.1 in the appendix along with the PCS criteria for each of those CLTs.

8.1.6.2 Selection of studies and analyses for overall drug-control comparisons

The group D pool was analyzed in the focus on outliers and shifts from normal to abnormal. Summaries were reviewed for patients whose CLTs met PCS criteria. Where rates of occurance of PCS CLTs exceeded placebo Fisher's Exact Test was applied to the data by this reviewer. The sponsor did not supply statistical testing of the outlier data.

The sponsor provided analyses of the group D pool of patients at all points where lab data was taken.

8.1.6.3 Standard analyses and exploration of laboratory data

8.1.6.3.1 Analyses focused on central tendency

The ISS presented a table of all the lab values that had significant mean changes from baseline. This table may be found in the appendix as table 8.1.6.3.1.1. There were no statistically significant mean changes that were clinically significant.

8.1.6.3.2 Analyses and exploration of data focused on outliers or shifts from normal to abnormal

The criteria for PCS may be found in the appendix in table 8.1.6.3.2.1. Tabulation of the number of patients who met PCS criteria at any time during the study divided by the number of patients who had a baseline and at least one post baseline measurement is found in table 8.1.6.3.2.2 in the appendix.

There were no PCS CLTs that occurred significantly more often with zaleplon than with placebo.

8.1.6.3.3 Dropouts due to abnormal laboratory values
Dropouts due to laboratory values are comparatively rare because in the greater part of the group D pool there were no laboratory values performed until the double blind treatment phase was over. Thus there were only four patients who dropped out due to abnormal laboratory results.

Eosinophilia
Patient 20512-0065-This 38- year- old woman was randomly assigned to the zaleplon 2 mg treatment group on 25 Nov 93. In her medical history, hypothyroidism (treated with levothyroxine and ferrosulfate) and allergy to nuts and pollen were reported, and she was taking several other drugs for other conditions (salicylate, phenazone, paracetamol, codeine, dextropropoxifene). On 19 Nov 1996 and 23 Nov 1993 (prestudy) her eosinophil count was 170/ mm3 (2.9 %) and 810/ mm3 (9.7 %) respectively (normal under 500/ mm3 or 6 %). The patient was considered as eligible for the study. On 26 Nov 1993, after night 1, the differential eosinophil count had increased to 900/ mm3 (12.5 %). The patient was withdrawn from the study after 2 nights of treatment because of this event. In poststudy measurements, on 28 Nov 1996 (1 day after) and 10 Jan 1996 (44 days after) the eosinophil count had decreased to 11% and 7% respectively.

Elevated liver function tests
Patient 30643-5510 This 68- year- old woman was assigned to receive open- label zaleplon 5 mg/ day on 28 Feb 1996. This patient had been randomly assigned to receive zaleplon 10 mg/ day on 10 Feb 1996 and completed double- blind treatment on 22 Feb 1996. Concomitant medications included salicylate 750 mg BID for arthritis, Legatrin PRN for leg cramps, and conjugated estrogens (0.625 mg)/ medroxyprogesterone (2.5 mg) as hormone replacement. On 29 Mar 1996, open label study day 30, the patient's SGOT was 263 U/ L (normal 9- 34 U/ L) and SGPT was 398 U/ L (normal 6- 34 U/ L). The patient's bilirubin and GTT values were within the normal range. On 30 Mar 1996, open label study day 32, study drug was discontinued. On 01 Apr 1996, the SGOT was 334 U/ L and the SGPT was 586 U/ L. Hepatitis panel was positive for Hepatitis C antibody was reactive and was confirmed reactive by repeat analyses. On 03 Apr 1996, the SGOT was 252 U/ L and the SGPT was 469 U/ L, but by 11 Apr 1996, the SGOT had decreased to 36 U/ L and the SGPT decreased to 98 U/ L. By 17 Apr 1996, the SGOT was within the normal range (32 U/ L) and the SGPT was only slightly elevated (50 U/ L). Both values had returned to the normal range by 20 May 1996. No symptoms were reported for the patient.

Patient 31228-0001-This 43- year- old woman was assigned to receive open- label zaleplon 10 mg/ day on 17 Jan 1996 and titrated to 20 mg/ day on 24 Jan 1996. This patient had been randomly assigned to receive zaleplon 10 mg/ day on 06 Dec 1995 in week 1 and 20 mg/ day on 13 Dec 1995 in week 2 in the double-blind study (patient 30716- 0011) and completed double- blind treatment on 20 Dec 1995. Her baseline SGPT was 50 U/ L (normal 6- 34 U/ L) and SGOT was 49 U/ L (normal 9- 34 U/ L). These had increased to SGPT 65 U/ L, and SGOT 62 U/ L on 15 Feb 1996 while on zaleplon 20 mg/ day. All other labs were normal. A hepatitis screen was positive for hepatitis C. The patient withdrew from the study on 18 Feb 1996, study day 33. She was referred to a liver specialist, who performed a liver biopsy that was consistent with active chronic hepatitis C. The patient had a history of IV drug abuse, jaundice, and long- standing slight elevation in SGOT.

Hyperglycemia
Patient 30814-0698-This 68- year- old man was assigned on 28 Feb 96 to receive zaleplon 10 mg. His medical history included, cardiac bypass surgery in 86. He was treated with vitamin B compound/ complex to compensate for a poor diet. This patient was a known diabetic without treatment since Aug 95. He completed the double blind phase, and continued into the open- label phase on 21 Mar 96 with 5mg of zaleplon until he was withdrawn for elevated blood glucose on 22 Apr 96. Hyperglycemia (mild severity, possibly drug related) is the only study event reported during the course of the study, and no treatment was given.

Summary of dropouts due to laboratory values
The patients with elevated liver function tests were positive for hepatitis C and the hyperglycemic patient had a standing history of diabetes mellitus. The patient with eosinophilia had no previous history to explain this laboratory value. The incidence of eosinophilia was numerically greater in the placebo group than in the zaleplon group but not statistically significant by Fishers Exact Test.

8.1.6.4 Additional analyses and explorations of laboratory data
None

8.1.7 Vital signs

8.1.7.1 Extent of vital sign testing in the development program
The ISS does not state the frequency at which vital signs were measured; however, the individual protocols in the studies which comprise group D were measured at screening, on the first day of single blind placebo (7 days before double blind drug was given), on the first day of double blind treatment, weekly during double blind treatment (whether it was a 14 or 28 day study), the day after the last dose of double blind treatment, and at follow-up 8-11 days after the last dose. Vital signs consisted for the most part of a 5 minute seated blood pressure, pulse, respiration and temperature the morning following awakening from the previous night's sleep. Weights were performed for the most part at entry and exit from the study.

8.1.7.2 Selection of studies and analyses for overall drug-control comparisons
The focus of the analysis is on the double blind, placebo controlled, parallel group, studies in group D.

8.1.7.3 Standard analyses and exploration based on vital sign data

8.1.7.3.1 Analyses focused on measures of central tendency
Table 8.1.7.3.1.1 contains the sponsor's summary of those vital signs which showed statistical difference from baseline. These changes were clinically insignificant and the zaleplon changes showed less mean perturbation than placebo. These analyses of central tendency do not reveal any changes in blood pressure, pulse, respiration, or temperature that are of clinical concern.

8.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal
The sponsor's criteria for clinically significant changes in vital signs follow in table 8.1.7.3.2.1.

Table 8.1.7.3.2.1 Criteria for determining potentially clinically significant changes in vital signs and weight	
Variable	Criteria a
Supine or sitting pulse rate	Increase of ≥ 15 beats/ min and rate ≥ 120 beats/ min or decrease of ≥ 15 beats/ min and rate ≥ 50 beats/ min
Supine, sitting, or standing systolic blood pressure	Increase of ≥ 20 mm Hg and pressure ≥ 180 mm Hg or decrease of ≥ 20 mm Hg and pressure ≤ 90 mm Hg
Supine, sitting, or standing diastolic blood pressure	Increase of ≥ 15 mm Hg and pressure ≥ 105 mm Hg or decrease of ≥ 15 mm Hg and pressure ≤ 50 mm Hg
Postural blood pressure change	Decrease of ≥ 25 mm Hg systolic or ≥ 10 mm Hg
Temperature	Increase of ≥ 1.1° C and temperature ≥ 38.3° C
Respiration rate	Increase or decrease of ≥ 50% and <10 or >25 breaths/ min
Weight	Change of ≥ 7% in body weight

a: Differences were measured from mean prestudy/ baseline values.

Table 8.1.7.3.2.2 in the appendix displays the number of patients in each treatment group who reached the levels of potentially clinically significance (PCS) described above. The sponsor did not provide statistical analysis of these occurance rates; therefore, this reviewer performed Fisher's Exact Tests on vital sign data where the occurrence rate of PCS events was greater for the "all zaleplon" group than that of placebo. There were no group differences in the number of patients who met PCS criteria that reached statistical significance by Fisher's Exact Test.

8.1.7.3.3 Dropouts for vital sign abnormalities

There was one dropout due to hypertension in the group D pool of patients. There were no dropouts for any other vital sign abnormality. Patient 30615-5402, taking zaleplon 10 mg, had a history of hypertension and a screening BP of 178/90. On day 8 of double blind treatment his BP was 194/94. He dropped out on day 12 with the complaint that the medicine made it difficult to regulate his blood pressure.

8.1.7.4 Additional analyses and explorations

There were no additional analyses or explorations of vital sign data performed by the sponsor.

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

The sponsor performed screening and baseline ECGs on patients in the phase III clinical trials. The sponsor went on to repeat the ECG at the follow-up visit which took place 8-12 days after the last dose. Therefore there is no systematically collected ECG data for patients in the phase III trials that is collected while

the patients are on drug or during acute withdrawal. The sponsor performed mean change from baseline analyses and exploration of outliers on this data set; however, this data shall not be reviewed because it is not a reflection of the potential ECG effects of zaleplon.

There are two phase I studies where ECGs were performed either while patients were on drug or the morning after. Patients received ECGs at 1.5 and 24 hours after dosing in study 101-UK. In this study there were 5 fixed single dose groups with 7 patients/group. Two patients in each group took placebo and the other five took zaleplon. The dose groups were 1, 5, 15, 30, and 60 mg. The sponsor stated that there were no ECG abnormalities at any time point at any dose group but did not provide any quantitative analysis of ECG parameters in the original NDA. This reviewer requested and received from the sponsor the individual ECG parameter data from study 101-UK. This data contained the individual patient values for PR, QRS, QT, and QTc for the ECGs performed at baseline, 1.5, and 24 hours post dose, plus the change from baseline values for each patient at each time point after dosing. Mean parameter values were calculated for each treatment group and its corresponding placebo group for each time point and mean change from baseline values were calculated for each time point for each dose group. Dose groups and ECG parameters were examined for any dose relationship to ECG parameter change. Visual inspection revealed no clinically significant changes in any individual or group in any parameter, and there was no dose relationship to any ECG parameter change (clinically significant or otherwise).

Patients in study 102-UK underwent ECG the day following zaleplon administration. Seventeen patients in two dose groups (15 mg n=7 zal, n=3 PBO; 30 mg n=4 zal, n=3 PBO) had no ECG abnormalities but the sponsor provided no quantitative analysis of ECG parameters with the NDA. The sponsor submitted on request mean change from baseline data for the same ECG parameters listed above in study 101-UK. There were no clinically significant changes in any parameter for individuals or groups.

8.1.9 Special studies

8.1.9.1 Memory impairment and residual effects

The sponsor performed two series of protocols to measure either day after dosing residual effects or memory effects. These studies were not necessarily mutually exclusive and this review therefore considers them together. Studies designated as studying residual effects used psychomotor testing to evaluate drug induced performance impairment at time points starting as early as 3.5 hours after dosing and extending to 14.5 hours after dosing. Protocols designated as memory studies examined time points from 1 to 8.25 hours post dosing. The DSST was used in most of these studies regardless of their stated purpose.

The sponsor performed three phase one studies to explore the effects of zaleplon on memory in comparison to placebo and various active comparitors. The sponsor pools the data from these three studies in their discussion of the memory impairment issue in the ISE; however, the studies are not easily pooled because of different designs, doses, and assessment schedules. This leads to some confusion; therefore, this review shall describe the of the individual studies separately and make qualitative conclusions about the memory and residual effect studies considered together.

Study 103-US was a double blind, placebo controlled, parallel group, single dose study of the effects of zaleplon (5,10, and 20 mg), triazolam (0.125, 0.25, and 0.5 mg) and placebo on memory, perception, and motor performance in 85 healthy male subjects age 20-45 years. Comparison of three doses of triazolam, three doses of zaleplon, and placebo revealed modest effects on memory and psychomotor function. Significant treatment effects were observed on only one of three memory tests and two of four psychomotor tests. When administered approximately 1 hour after drug administration, the visual recognition span test (a measure of memory function) revealed significant decrements in the 10- and 20- mg zaleplon dose groups and in all three triazolam dose groups (0.125, 0.25, and 0.5 mg). The DSST revealed psychomotor deficits 1 hour after administration of 10 mg zaleplon, 0.25 mg triazolam, and 0.5 mg triazolam. Significant psychomotor impairment was also apparent on the Purdue pegboard test the morning after administration of 0.25 mg triazolam. Only the 5 mg dose of zaleplon failed to produce any significant differences from placebo. Thus, the pharmacodynamic profiles of zaleplon and triazolam were similar.

Study 108-UK was a single dose, double blind, three period

crossover study of the effects of zaleplon 20 mg, lorazepam 2 mg, and placebo on memory in 12 healthy male adult subjects aged 18-35 years. Performance on a comprehensive battery of tests of psychomotor and memory function, as well as subjects' self-ratings of mood and bodily functions were assessed before drug administration and at 1, 3, and 5 hours after drug administration. Tests included working memory tests: digit span test, mental rotation test, and Baddeley reasoning test; secondary memory tests: free recall test, prose recall test, and Baddeley's semantic retrieval test; and psychomotor tests: focused attention, symbol copying test, digit symbol substitution test, tapping rate, critical flicker fusion, pursuit rotor test, and rapid information processing test. For most of the tests, the effects of zaleplon on memory and the results of psychomotor tests and subjects' self- ratings were qualitatively similar to those of lorazepam and different from placebo at 1 hour after drug administration, but subjects treated with zaleplon recovered by 3 hours. Impairments induced by lorazepam often persisted throughout the 5- hour testing sessions.

Study 122-US was a double-blind, placebo controlled, crossover study of the effects of zaleplon (10 and 20 mg), zolpidem (10 and 20 mg), triazolam (0.25 mg), and placebo on memory and psychomotor performance in 23 healthy men and women aged 18-45 years. A battery of pharmacodynamic tests was administered to each subject predose, and at 1. 25 and 8. 25 hours after administration. Subjects were awakened approximately 15 minutes before each of the two postdose test batteries. The test battery was administered in the following order: Subjective Effects Questionnaire, Immediate Word Recall Test (1. 25- hour observation only), Digit Span Test, Digit Symbol Substitution Test, Paired- Associates Learning Test, Divided- Attention Test, observer- rated Questionnaire, and Delayed Word Recall Test (1. 25- hour and 8. 25- hour observations only). Compared with placebo, the zaleplon 10- mg treatment did not produce significant effects on memory, learning, or psychomotor performance in the 1. 25- hour test battery. The zolpidem 10- mg and zaleplon 20- mg treatments produced a moderate impairment on short- term and long- term memory (Word Recall), learning (Paired Associates Test), and visuomotor coordination and vigilance (Tracking and Variability components of the Divided Attention Test), and the magnitude of impairment was similar for these two treatments. The triazolam 0. 25- mg treatment produced a moderate impairment on memory (Word Recall) which was similar to the effects of the zolpidem 10- mg and zaleplon 20- mg treatments. However, unlike the zolpidem 10- mg and zaleplon 20- mg treatments, the triazolam 0. 25- mg treatment did not

affect learning (Paired Associates Test) and the Tracking and Variability components of the Divided Attention Test. The triazolam 0. 25- mg treatment and the zaleplon 20- mg treatment had similar effects on the Digit Symbol Substitution Test. By the following morning, the majority of the impairment produced by the active treatments had returned to placebo levels. The triazolam 0. 25- mg and zolpidem 20- mg treatments produced small, but statistically significant, residual effects on the Digit Symbol Substitution Test. Additionally, all active treatments produced significant differences from placebo in Delayed Word Recall Test scores. The effects of the zolpidem 10- mg, triazolam 0. 25- mg, and zaleplon 20- mg treatments on the 8. 25- hour Delayed Word Recall Test were equivalent.

The sponsor makes reference to three protocols studying next day residual psychomotor effects plus one study of driving impairment that is reviewed in section 8.1.9.2.

Study 124-US was designed to study the day-after-dose residual effects of zaleplon 10 and 20 mg, flurazepam, and placebo in 93 healthy men and women volunteers. This was a single dose, double blind, placebo controlled, crossover study. The primary outcome variable was the mean sleep latency test (MSLT) measured 9.5 and 14.5 hours after dosing. Secondary outcome variables included the subjective assessment of sedation from the visual analogue scale; tracking deviation, missed stimuli, and response times from the divided attention task (DAT); the total number of pairs completed and the total number of pairs correctly completed from the digit symbol substitution test (DSST); and the number of symbols copied and the number of symbols correctly copied from the symbol copying test (SCT). MSLT times for both zaleplon groups were not significantly different from those for the placebo group at any evaluation or overall. In contrast, sleep latency times were significantly shorter for the flurazepam group than for the placebo group or for either zaleplon group at each evaluation and overall. The number of pairs completed and the number of pairs completed correctly on the DSST for both zaleplon groups were not significantly different from those for the placebo group at any evaluation except during the first session when the number of pairs completed and the number completed correctly were higher in the zaleplon 20 mg group than in the placebo group. The number of pairs completed and the number completed correctly were significantly greater in both zaleplon groups than in the flurazepam group during the second session and overall.

Study 208-US was a double blind, placebo and active controlled,

two dose, randomized three-way crossover study of 36 men and women with sleep maintenance insomnia. The primary variable for evaluating residual sedation was the median daytime sleep latency determined from a SLT that was conducted 5 hours (session 1) and 6.5 hours (session 2) hours after dose administration. Other variables included measures of psychomotor performance (digit symbol substitution test, DSST; symbol copying test, SCT) and subjective ratings of sedation (visual analog scale, VAS). Secondary efficacy evaluations were conducted by using sleep variables derived from PSG recordings and responses to postsleep questionnaires. Zaleplon treatment did not differ significantly from placebo for any measure of residual sedation at 5 and 6.5 hours after dose administration. In contrast, patients were significantly impaired on all measures of residual sedation for at least 6.5 hours after flurazepam treatment.

Study 143-US was a double blind, placebo controlled, incomplete block crossover study of 36 healthy men and women aged 18-45 years. Subjects participated in the study for up to 32 days and received 6 single doses separated by a 48- hour washout period between doses. Before this, subjects had undergone a training session and 2 acclimation nights. The analyses were made on the choice reaction time (CRT) and critical flicker fusion (CFF) threshold, digit symbol substitution test (DSST), Sternberg memory scanning test (SMST) and an immediate and delayed recall of a word list. The effects of zolpidem 10 mg, given during the night 2, 3, 4 or 5 hours before awakening, were detectable the morning after on most of the tests and subjective scales. In contrast to this, zaleplon 10 mg produced no measurable nor subjective effects.

In summary, zaleplon has similar effects on memory as two short acting benzodiazepines and zolpidem. The duration of these effects also appears to be dose dependent. The effects of zaleplon 10 mg on measures of psychomotor function are for the most part absent at time points of four hours or more after dosing; however, this is not necessarily so for zaleplon 20 mg. The above protocols tested zaleplon 20 mg only at time points of 1.25, 8.25, 9.5, and 14.5 hours after dosing. There were no differences between zaleplon 20 mg and placebo at 8.25 hours post dose and beyond. Study 134-NE described below examine driving ability after taking zaleplon 10 and 20 mg at the time points of 5 and 10 hours post dose. Other wise there is little evidence for lack of memory and residual effects of zaleplon 20 mg at time points less than 8.25 hours post dosing.

From a safety standpoint, these studies demonstrate that there is

a difference between zaleplon and placebo with respect to memory parameters. Comparative claims that zaleplon produces less cognitive dysfunction than the comparitor drugs should not be implied in labeling. These studies were relatively small and did not include an efficacy analysis. One can not, therefore, make conclusions about the relative safety of zaleplon with respect to the comparitor if one can not make simultaneous comparisons with regard to efficacy.

8.1.9.2 Automobile driving

Study 134-NE was a phase I randomized, double blind, placebo/active drug controlled, crossover study designed to explore the effects of zaleplon (10 and 20 mg), zopiclone 7.5 mg, and placebo on driving ability and memory in 29 healthy men and women aged 22-40 years. The primary pharmacodynamic variable was the standard deviation of lateral position (SDLP). Zopiclone 7.5 mg affected car driving performance when given 5 or 10 hours before driving sessions and affected equilibrium when given 5 hours before. Ten and 20- mg doses of zaleplon given 5 or 10 hours before did not significantly affect car driving ability or equilibrium.

8.1.9.3 Respiratory effects

The effects of zaleplon on respiration and respiratory drive were studied in three phase I protocols (112-UK, 120-CA, and 133-GE). Controlled trials of acute administration of zaleplon 10 mg in patients with chronic obstructive pulmonary disease or moderate obstructive sleep apnea showed no evidence of alterations in blood gases or apnea/ hypopnea index, respectively.

8.1.9.4 Effects on sleep stages

The sponsor states in the draft labeling that zaleplon preserves stages of sleep and sites protocols 203-US, 204-EU, and 205-EU/CA. All of these studies were randomized, double blind, placebo controlled, parallel group, sleep laboratory studies in patients with primary insomnia. The three studies had varying durations; 203 was 14 days, 204 was 28 days, and 205 was 5 days in duration.

Summary data for sleep stage percentage is given in study 203; however, there is no statistical analysis for these data. The sponsor states that there are no "important" differences between zaleplon and placebo, yet there likewise appears to be no important differences between triazolam and placebo or triazolam and zaleplon. If there were a statistically significant difference between zaleplon and triazolam in addition to a difference between triazolam and placebo with no difference

between zaleplon and placebo then this claim would be perhaps acceptable. In this case, it is not supported; it is perhaps only suggested.

Study 204 compares doses of zaleplon 10 and 20 mg against placebo and zolpidem 10 mg. There are statistically different percentages of time spent in sleep stages between placebo and the zaleplon 20 mg group. There is also no consistent difference between zaleplon and zolpidem when zaleplon is statistically indistinguishable from placebo. This study does not support the claim that zaleplon preserves sleep stages.

Study 205 has no active comparitor. The implied statement is that zaleplon does not disturb sleep stages (and architecture) as other hypnotics historically do. Since there is no active comparitor against which zaleplon may show a difference, study 205 is not designed to address this question.

8.1.10 Withdrawal phenomena and abuse potential

A detailed review of the sponsor's exploration of zaleplon's potential for treatment withdrawal syndromes may be found in section 8.1.4.1-3. Abrupt withdrawal from zaleplon at doses up to 20 mg/day for 28 days produced only mild rebound insomnia. There was no evidence of vital sign perturbations (hypertension, tachycardia), neurologic signs (tremor, seizures), or mental status changes (delirium, confusion, hallucinations, anxiety).

The sponsor performed two phase I studies to explore zaleplon's potential to be abused (104-US and 110-US). Study 104 exposed patients with a documented history of sedative hypnotic abuse to triazolam and zaleplon with the goal to measure cognitive impairment, sedation, and equivalence with regard to sedation. It was estimated that zaleplon 25, 50, and 75 mg were equivalent to triazolam 0.25, 0.50, and 0.75 mg. Study 110 took these results and applied them in a crossover design to measure zaleplon's abuse potential by comparing the subjective effects of zaleplon to triazolam and placebo using the Addiction Research Center Inventory (ACRI). The mean responses for each of the indirect measures of drug reinforcement on the next- day questionnaire: subject ratings of "like to take drug again," "worth on the street," and "willing to pay on the street" were statistically significantly different than placebo at the dose condition for each of these measures ($p < 0.05$). Zaleplon and triazolam generally increased these ratings as a function of dose. In the case of "like to take drug again," the two highest doses of triazolam significantly increased these ratings above placebo levels, whereas all doses of zaleplon did so ($p < 0.05$).

In the case of "worth on the street" and "willing to pay on the street," the highest dose of each drug increased these ratings significantly above levels observed with placebo. Zaleplon and triazolam produced comparable effects on these measures, the results for corresponding doses did not differ significantly. Zaleplon shows a similar abuse potential to triazolam.

8.1.11 Human reproduction data

Studies to assess the effects of zaleplon on human reproduction and development have not been performed. Six (6) unintended pregnancies and 1 case of vaginal hemorrhage (30120- 4217, placebo group), that was considered a possible miscarriage, occurred during Phase II/ III studies. Five(5) of the pregnancies occurred in patients who had received zaleplon and 1 in a placebo patient (30127- 4157). One (1) of the zaleplon-treated patients (30110- 4781) conceived approximately 1 month after her last dose of zaleplon; she delivered a healthy, full-term baby. Of the 4 pregnancies that occurred in patients during zaleplon treatment, 1 resulted in the delivery of a healthy baby (patient 30130- 4710), 1 ended in spontaneous abortion (30106-4483), 1 patient (20521- 0164) had an elective abortion, and 1 patient (30716- 0005) had a tubal pregnancy that was terminated.

8.1.12 Overdose experience

There were 2 cases of overdose during clinical trials of zaleplon. 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.

Signs and symptoms of zaleplon overdose appear to resemble those of other benzodiazepine and non-benzodiazepine sedative hypnotics, namely sedation, drowsiness, mental confusion, ataxia, and lethargy. More severe cases of zaleplon overdose may lead to hypotonia, hypotension, respiratory depression, coma, and in the extreme, death.

Zaleplon and ethanol potentiate each other's cognitive and sedating effects. Therefore overdose of zaleplon in the presence of ethanol or other sedating drugs would likely increase sedative and neurological symptoms seen with these drugs when taken individually in excessive amounts.

Zaleplon clearance is decreased in patients with impaired hepatic function and is not recommended for patients with severe hepatic insufficiency. Patients with mild to moderate insufficiency shall be more susceptible to symptoms of overdose due to increased blood levels of zaleplon.

Animal studies suggest that flumazenil is an antagonist to zaleplon and therefore may be of use in the treatment of overdose. There is no human experience with the use of flumazenil in human overdose of zaleplon to this date.

8.2 Adequacy of patient exposure and safety assessments

8.2.1 Adequacy of clinical exposure

The International Committee on Harmonization Efficacy Guidelines (ICH) state that an adequate number of patients should be exposed to a drug intended for the long term treatment of non-life threatening illnesses to offer reasonable assurance that the drug is safe for the long term treatment of the intended illness. The Committee established that 1500 patients total (including short term studies), 300-600 patients for 6 months, and 100 patients for one year exposed to dosages intended for clinical use represented an acceptable safety database.

The zaleplon development program meets and exceeds these requirements except for the number of patients exposed for one year (see section 5.1.3). Only 59 patients had been exposed for up to one year; however, zaleplon is not to be used as a long term treatment agent. The sponsor's development program's clinical exposure exceeds the planned use of the drug.

A broad range of patients were exposed to zaleplon. Studies focusing on the elderly and patients aged 18-65 were performed. Within those studies, adequate numbers of men and women were exposed. Care was taken to analyze for age, sex, and ethnicity differences.

There was no pediatric development program.

8.2.2 Adequacy of animal or in vitro testing

Animal and in vitro testing appear to be adequate. The major finding of withdrawal seizures in higher doses administered to

animals suggests that seizures and a more serious withdrawal syndrome may be seen in humans who abuse or over dose on high doses of zaleplon. These types of reactions have not been seen in humans in extended zaleplon use at 20 mg/day or in acute overdose.

8.2.3 Adequacy of routine clinical testing
Routine clinical testing including vital signs, clinical chemistry, hematology, and urinalysis were adequately studied. The collection of ECGs in the phase III studies does not reflect the effect of zaleplon on the electrical conduction of the heart.

There is one phase I study (study 101-UK) where ECGs are performed on subjects 1.5 and 24 hours after taking zaleplon. Doses of 1, 5, 15, 30 and 60 mg were given. 60 mg represents three times the upper limit of the recommended dose for adults and six times the upper limit for the elderly. There was no dose relationship to changes in any ECG parameters (PR, QRS, QT, QTc) and there were no clinically significant changes in the ECGs.

This class of drugs is not connected with cardiac conduction abnormalities. Therefore, extensive studies of cardiac conduction are not necessary since there is no suggestion of conduction defects in the animal data or a quantitative analysis of ECG parameters in study 101.

8.2.4 Adequacy of metabolic work up.
At the time of this report, the biopharmacology review is pending. Therefore, this reviewer shall reserve comment on the completeness of the sponsor's metabolic work up of zaleplon at this point.

8.2.5 Adequacy of evaluation for potential adverse events
This drug class carries the increased potential risk for cognitive dysfunction, memory, amnesia, respiratory depression, rebound insomnia, withdrawal phenomena, sedation, rebound anxiety, and abuse liability. All of these potential adverse events were adequately studied.

8.2.6 Assessment of quality and completeness of data
The data appears to be complete. Patient profiles accurately match comments in the CRFs. Annotations and corrections to the CRFs, when done, are clearly marked, initialed, and the reason for the editing is clearly explained and appropriate.

8.3 Summary of selected drug related adverse events
8.3.1 Hallucinations

Zaleplon related hallucinations occurred rarely and at the same rate at which hallucinations occurred in active comparitors (13/2831 [0.45%] zaleplon vs 3/560 [0.53%] all other comparitors. The severity, character and duration of the hallucinations are described in section 8.1.2.1. They are hypnogogic and in almost all cases did not seem to trouble the patients by their presence. The hallucinations were self limited and had resolved by the next morning.

Interestingly, women reported hallucinations statistically more often than men while men reported "abnormal thinking" more often than women (see section 8.1.5.5.2.1).

8.3.2 Amnesia

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 that were judged by this reviewer as likely to be related to either zaleplon or zolpidem. The period of amnesia was isolated to periods of time surrounding dosing and duration of the drug. Amnesia occurred at higher doses (20 mg) more often than at 5 or 10 mg. The reporting frequency was also significantly related to dose via linear trend analysis (p=0.002). The quality and duration of zaleplon associated amnestic episodes is described in section 8.1.2.2.

8.3.3 Dizziness, ataxia

There were rare cases (3/2831) of dizziness and ataxia reported with zaleplon; there were no cases of dizziness reported in the placebo groups (n=1028). The quality and duration of the ataxia is described in section 8.1.2.3. Ataxia and dizziness was especially prominent in patients who took zaleplon but then did not go to bed. This practice is clearly outside of the parameters of use of the drug.

8.3.4 Depression

3/2831 (0.1%) patients reported depression in the non-Japanese development program. The depression was mild and resolved with discontinuation. One patient in the Japanese study groups completed suicide. This occurred while he was taking zolpidem and he was 4 days post zaleplon treatment. The other three cases of depression resolved within one day of discontinuation of zaleplon. It is unlikely that the suicide was zaleplon related; however, it seems likely that the other three cases were related to zaleplon due to their temporal association to drug dosing.

The sponsor did not have Zung depression scale data either during

or immediately after the study. The Zung Depression Scale was used merely as a screening tool. Fisher's Exact Testing did not reveal any significant difference between placebo, comparitor, or zaleplon groups with regard to treatment emergent depression.

Treatment emergent depressed mood is a well documented phenomenon that is associated with sedative hypnotic use. There is no suggestion that the frequency or severity of treatment emergent depressed mood is greater with zaleplon than with other agents.

8.3.5 Withdrawal phenomena

Abrupt discontinuation of zaleplon at doses of 20 mg/day for up to 28 days did not produce any serious withdrawal symptoms. Mild rebound insomnia occurred at a significantly higher rate in zaleplon patients as opposed to placebo but this difference was only present during the first night after discontinuation (see section 8.1.4.2).

Animal studies did produce evidence that withdrawal from zaleplon at higher doses (20 mg/kg/day) may produce fatal withdrawal syndromes. This dose is 70 fold higher than the highest recommended dose in humans. There were no perturbations in vital signs, tremulousness, or hallucinations upon withdrawal of zaleplon in phases I-III of the development program. Though it has yet to be observed in humans, withdrawal seizures, hallucinations, and vital sign perturbations may be seen in the case of overdose or chronic abuse.

8.3.6 Headache

Headache was the most commonly reported adverse event with zaleplon. It did not meet criteria for common and drug related, but was significantly related to dose [(p=0.03) see section 8.1.5.5]. ~~Headache was the second most common reason for~~ dropout in both short and long term studies yet the drop out rate was not significantly different from that of placebo (see section 8.1.3.2).

8.3.7 Sedation/Somnolence

Somnolence is an exaggeration or undesirable prolongation of the clinical effect. It was the most common reason for dropout in the short term clinical studies, yet this did not reach a significant difference from placebo (see section 8.1.3.2).

9.0 Labeling review

This review of the sponsors proposed draft labeling covers the "special populations", "concentration-effect relationship", and

the "postulated relationship between elimination rate of hypnotics and their profile on common untoward effects" subsections of the pharmacokinetic section, the "controlled studies supporting safety and efficacy", and all sections thereafter.

The subsections mentioned above in the pharmacokinetics section are accurate as written.

The second paragraph of the subsection entitled transient insomnia (draft labeling page under the "controlled studies supporting safety and efficacy" section) should be deleted. Study 209, which ostensibly supports this indication, did not have a positive outcome. Latency to persistent sleep (LPS) and sleep efficiency during the first four hours of sleep were the primary efficacy variables. LPS was not distinguishable from placebo in this study. The first paragraph, that sites study 210 is accurate as it stands.

In the subsection "chronic insomnia" (pages 5 and 6, draft labeling), references to efficacy measures other than time to sleep onset (TSO) should be avoided. Though subjective measures of sleep duration (total time slept [TTS]) were significantly longer than placebo at 20 mg/day, they were not at 5 and 10 mg/day in study 303. TTS was a secondary variable as was sleep quality. Similarly, TSO and LPS were the primary variables in the studies sited in this section. Many secondary variable were negative except for the doses and times that the sponsor mentions. Since there was no correction for multiple comparisons and there is no description of study design in the labeling, then the reader has no way of judging the results of these secondary variables in the context of the study.

The subsection entitled "Effects on sleep stages" should be deleted (see section 8.1.9.4).

The opening sentence in the subsection "Next-day residual effects" should be rephrased (see section 8.1.9.1). A more accurate statement would be that next day residual hypnotic effects were indistinguishable from placebo. Zaleplon has similar effects on memory as two short acting benzodiazepines and zolpidem. The duration of these effects also appears to be dose dependent. The effects of zaleplon 10 mg on measures of psychomotor function are for the most part absent at time points of four hours or more after dosing; however, this is not necessarily so for zaleplon 20 mg. The protocols described in

section 8.1.9.1 tested zaleplon 20 mg only at time points of 1.25, 8.25, 9.5, and 14.5 hours after dosing. There were no differences between zaleplon 20 mg and placebo at 8.25 hours post dose and beyond.

The subsection on rebound insomnia is accurate but minimizes the rebound effect (see section 8.1.4.2).

The subsection on memory impairment states that there was no memory impairment after four hours at the recommended dose; this is somewhat misleading. They go on to site data for the 10 mg dose (not 10 and 20 mg). The dosing and administration section lists the recommended dose at 10 mg for adults and 5 mg for patients over the age of 65 years; however, the section on studies supporting efficacy and safety extensively sites data for 20 mg dosing. This implies that zaleplon is both safe and effective at the 20 mg/day dose but allows the sponsor to selectively describe the drug's benefits and untoward effects at the lower dose. Labeling should consistently report both the safety and efficacy data for the dose the sponsor lists as the recommended dose.

While there is no memory impairment in the 10 mg dose at 1.25 hours after dosing, there was in the 20 mg group. Zaleplon 20 mg was not tested for memory impairment at time points between 1.25 and 8.25 hours (see section 8.1.9.1).

The indications, contraindications, warnings, and precautions sections are accurate as written.

The section "Information for patients" states, "Sonata is used to treat different types of sleep problems, such as: trouble falling asleep, waking up too early in the morning, waking up often during the night...". Zaleplon's efficacy was established based on significant decreases in time to sleep onset (improving trouble falling asleep). Zaleplon was usually no better than placebo at decreasing the number of awakenings (waking up too often during the night), and was intermittently more effective than placebo at increasing total time slept (waking up too early). This detailed breakdown of the types of insomnia give the impression that zaleplon is effective at treating all of the symptoms that are reported under the rubric of insomnia when, in fact, of the three symptoms listed, it is only consistently effective at helping people fall asleep. Zaleplon's contribution to the hypnotic armamentarium is its short half-life, which pharmacodynamically leads to fewer problems (or benefits as the case may be) with people awakening in the morning. This section

needs to be modified to either accurately reflect zaleplon's potential therapeutic strengths and weaknesses or made more general so as not to claim greater therapeutic capabilities than the data supports.

In the subsection "Changes in behavior and thinking" under the "Information to patients" section (page 11) the sponsor states that the adverse event "loss of personal identity" occurs rarely with hypnotic use. This adverse event term is unclear (e.g. does it mean depersonalization or perhaps fugue) and either should be changed or deleted.

In the section "Ability to drive or use machines" (page 16 draft labeling) the sponsor sites data stating that there was no driving impairment 5 hours after taking zaleplon. In the information for patients section the sponsor states that zaleplon should be taken only if one has four hours before which being awake is necessary. These two sections are inconsistent. Since driving and operating machinery safely is one of the greater concerns with hypnotic use, then it would be better to state that patients should not take zaleplon unless they have 5 hours before they need to be awake or alert.

The adverse reaction section should be condensed. The narrative section on page 17 describing tabular data is long and redundant. Presenting two different pools of data for 1 % adverse event data is not necessary. The 28 day controlled trial pool is the most informative because it tracks not only adverse events from short term use but adverse events that occurred when zaleplon was used for up to 28 days. Table 1 on page 18 should be deleted and table 2 should be the only 1% adverse event table.

The narrative listing of other adverse events (page 20 of draft labeling) contains events that were already listed previously in the 1% tables. This listing should only include events that are not discussed in previous sections.

10.0 Conclusions

The NDA provides a body of evidence to support zaleplon as a safe and effective hypnotic drug to be used in the treatment of insomnia. The sponsor must either decide to list efficacy data for 10 mg/day dosing or modify the safety information to reflect adverse events and other safety data reflecting 20 mg/day dosing. (See section 9.0)

11.0 Recommendations

From a clinical standpoint, I recommend that zaleplon be approved

as a safe and effective treatment for insomnia after clarification of labeling issues.

/S/ [redacted] 7/14/98

Paul J. Andreason, M.D.
Medical Review Officer
Division of Neuropharmacologic Drug Products

11-10-98

I agree that there is sufficient evidence of safety + effectiveness to issue an approvable letter. See memo to file for more detailed comments.

/S/ [redacted]

TL, PNP

APPEARS THIS WAY ON ORIGINAL

APPENDICES

Table 5.1.1.1 Clinical Studies of Zaleplon			
Protocol No. Start/ Stop Date	**Study Design**	**Study Drug Dose, Route, Duration**	**Enrolled ITT / Safety**
0897A1- 101- UK 4/ 90- 6/ 90	Phase I, double- blind, placebo-controlled, single dose, pharmacokinetic, safety and tolerability study of zaleplon doses of 1-, 5-, 15- , 30- and 60- mg	Zal 1 mg, oral, SD Zal 5 mg, oral, SD Zal 15 mg, oral, SD Zal 30 mg, (2 X 15 mg), oral, SD Zal 60 mg (4 X 15 mg), oral, SD Placebo, oral, SD	37/ 35
0897A1- 102- UK 10/ 90- 11/ 90	Phase I, double- blind, placebo-controlled, pharmacokinetic, safety and tolerability study of zaleplon doses of 15- and 30- mg over a 10- day period	Zal 15 mg, oral, QD x 10 days Zal 30 mg (2 x 15 mg), oral, QD x 10 days Placebo, oral, QD x 10 days	24/ 20
0897A1- 103- US 8/ 93- 11/ 93	Phase I, randomized, comparative, double- blind, parallel- group, single-dose study of the effects of Florino zaleplon (5, 10, and 20 mg), triazolam (0.125, 0.25, and 0.5 mg), and placebo on memory and psychomotor tests and the perception of sedation in healthy male subjects	Zal 5 mg, oral, SD Zal 10 mg, (2 X 5 mg), oral, SD Zal 20 mg (1 X 5 mg +1 X 15 mg), oral, SD Triazolam 0.125 mg, oral, SD Triazolam 0.25 mg, oral, SD	85/ 85
0897A1- 104- US 2/ 94- 4/ 94	Phase I, double- blind, SD, ascending dose assessment of the effects of zaleplon and triazolam on measures of behavioral effects and abuse liability in subjects who had histories of sedative drug abuse	Zal 10 mg (2 X 5 mg), oral, SD Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, SD Zal 40 mg (2 X 5 mg + 2 X 15 mg), oral, SD Zal 60 mg (4 X 15 mg), oral, SD Zal 75 mg (5 X 15 mg), oral, SD Triazolam 0.25 mg, 0.50 mg, 0.75 mg, oral, SD Placebo, oral, SD Zal 13 C- and 14 C- labeled (20- mg in 150- mL of solution), oral, SD	6M
0897A1- 105- US 8/ 93- 10/ 93	Phase I, open- label, single- dose, mass balance , pharmacokinetic and metabolic profile study with 13 C- and 14 C- radiolabeled zaleplon administered orally to healthy adult male subjects	Zal 13 C- and 14 C- labeled (20- mg in 150- mL of solution), oral, SD	6M
0897A1- 106- US 9/ 93- 10/ 93	Phase I, double- blind, placebo-controlled, SD, pharmacokinetics and safety and tolerability study of zaleplon in healthy, elderly subjects (65- 75 yrs) Each subject received ascending doses (5, 10, 15, and 30 mg) of zaleplon and one dose of placebo according to one of the five treatment sequences.	Zal 5 mg, oral, SD Zal 10 mg (2 X 5 mg), oral, SD Zal 15 mg (1 X 15 mg), oral, SD Zal 30 mg (2 X 15 mg), oral, SD Placebo, oral, SD	20/20
0897A1- 107- US 3/ 94- 6/ 94	Phase I, open- label, randomized, 2-period crossover, pharmacokinetics study of 5- mg and 10- mg doses of zaleplon in healthy young (18- 45 yrs) and elderly (65- 80 yrs), male and female subjects for assessment of age/ sex characteristics	Zal 5 mg, oral, SD Zal 10 mg, (2 x 5 mg), oral, SD	34/34
0897A1- 108- UK 9/ 91- 3/ 92	Phase I, comparative, double- blind, placebo- controlled, single- dose, 3-period crossover study of 20 mg of zaleplon and 2 mg of lorazepam on memory and psychomotor effects in healthy men The protocol was ammended to include 20 mg rather than 40 mg of zaleplon. Excessive pharmacological activity including somnolence, confusion, and speech disorder was reported in the 3 subjects who had already completed the study with 40 mg of zaleplon. Therefore, the dose of zaleplon was reduced to 20 mg.	Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, SD Zal 40 mg (2 X 5 mg + 2 X 15 mg), oral, SD Lorazepam 2mg, oral, SD Placebo, oral, SD	20/20

Table 5.1.1.1 Clinical Studies of Zaleplon			
Protocol No. Start/ Stop Date	**Study Design**	**Study Drug Dose, Route, Duration**	**Enrolled ITT / Safety**
0897A1- 109- US 11/ 94- 2/ 96	Phase I, double- blind, placebo-controlled, randomized, 6- period crossover drug interaction study of zaleplon (10 mg) or triazolam (0.25 mg) with or without ethanol on behavioral effects	Zal 10 mg (2 X 5 mg), oral, SD Zal 10 mg (2 X 5 mg), + ethanol, oral, SD Triazolam 0.25 mg, oral, SD Triazolam 0.25 mg + ethanol, oral, SD Placebo, oral, SD Placebo + ethanol, oral, SD	19/ 19
0897A1- 110- US 8/ 94- 4/ 96	Phase I, comparative, double- blind, placebo- controlled, SD, randomized, 7-period crossover study of zaleplon (25, 50, and 75 mg) and triazolam (0.25, 0.50, and 0.75 mg) on measures of behavioral effects and abuse liability with illicit sedative drug users	Zal 25 mg (2 X 5 mg + 1 X 15 mg), oral, SD Zal 50 mg (1 X 5 mg + 3 X 15 mg), oral, SD Zal 75 mg (5 X 15 mg), oral, SD Triazolam 0.25, 0.50, 0.75 mg, oral, SD Placebo, oral, SD	16/ 16
0897A1- 111- UK 2/ 94- 3/ 94	Phase I, open label, randomized, SD, 2-period crossover relative bioavailability study of two oral formulations of zaleplon	Zal 10 mg (2X 5 mg), oral, SD capsules Zal 10 mg, oral, SD tablets	20/ 20
0897A1- 112- UK 5/ 94- 7/ 94	Phase I, comparative, double- blind, placebo and positive- controlled, single dose, 3- period crossover Hanning study on safety, tolerability and respiratory effects study of zaleplon compared to morphine (as a standard index of respiratory depression) in healthy men	Zal 20 mg (1 X 5 mg +1 X 15 mg), oral, SD Morphine sulphate, 10 mg, SD, IM Placebo, IM for morphine Placebo, oral, SD for zal	12/ 12
0897A1- 113- GE 4/ 94- 4/ 94	Phase I, open- label, randomized, 2-period 26639 crossover, bioavailability study of 10 mg zaleplon in Dietrich fasting and postprandial states in healthy adults	Zal 10 mg (2 X 5 mg), oral, SD	20/ 20
0897A1- 114- US 10/ 95- 11/ 95	Phase I, open- label, non- randomized pharmacokinetics study to determine the excretion of zaleplon and 5- oxo-zaleplon, (M2 metabolite) in breast milk in healthy lactating women	Zal 10 mg, oral, SD	5/ 5
0897A1- 115- FR 3/ 95- 4/ 95	Phase I, open- label, partially randomized, SD, 4- period crossover. absolute bioavailability and safety study.	Zal 1, 2.5, 5 mg, IV, SD Zal 5 mg, oral, SD	32/ 32
0897A1- 116- UK 10/ 94- 10/ 95	Phase I, open- label, nonrandomized, SD, pharmacokinetics study of zaleplon in healthy subjects and individuals with hepatic impairment	Zal 10 mg (2 X 5 mg), oral, SD	30 (12 subjects, 18 patients)/ 30
0897A1- 117- GE 5/ 94- 9/ 96	Phase I, open- label, parallel, multicenter study of the safety, tolerance, and pharmacokinetics of a single- dose of zaleplon, in healthy subjects and individuals with renal impairment	Zal 10 mg (2 X 5 mg), oral, SD	54 (25 subjects, 29 patients)/ 54
0897A1- 118- UK 9/ 94- 10/ 94	Phase I, open- label, (multiple- dose, nonrandomized, single sequence, 2-period McEwen crossover, pharmacokinetics and pharmacodynamics drug interaction study of zaleplon with warfarin in healthy adult males	Zal 20 mg (1 X 5 mg + 15 mg), oral, QD X 12-days Study day 6 - 13. Warfarin 25 mg, oral, QD X 2- days; Study day 1 and 13	12/ 12
0897A1- 119- US 8/ 94- 9/ 94	Phase I, open- label, randomized, 4-period crossover, bioequivalence study of 4 oral formulations of zaleplon in healthy men.	Zal 10 mg (2 X 5 mg), oral, SD, capsule Zal 10 mg (1 X 10 mg), oral, SD, capsule Zal 10 mg (1 X 10 mg), oral, SD, direct compression tablet Zal 10 mg (1 X 10 mg), oral, SD[redacted]	36/ 36

Table 5.1.1.1 Clinical Studies of Zaleplon			
Protocol No. Start/ Stop Date	**Study Design**	**Study Drug Dose, Route, Duration**	**Enrolled ITT / Safety**
0897A1- 120- CA 9/ 95- 9/ 96	A multicenter, single- dose, randomized, double- blind, placebo- controlled, crossover, safety and efficacy study of 10 mg zaleplon, 10 mg zolpidem, and placebo in adult outpatients with insomnia and chronic obstructive pulmonary disease (COPD)	Zal 10 mg (1 X 10 mg), oral, SD Zolpidem 10 mg, oral, SD Placebo, oral, SD	31/ 31
0897A1- 121- US 4/ 96- 9/ 96	Phase I, double- blind, placebo-controlled, 5- period crossover, pharmacokinetic/ pharmaco- dynamic study of 10 and 20 mg doses of zaleplon and 10 and 20 mg doses of zolpidem in healthy young adults with quantified EEG	Zal 10 mg (1 X 10 mg), oral, SD Zal 20 mg (2 X 10 mg), oral, SD Zolpidem 10 mg, 20 mg, oral, SD Placebo, oral, SD	11/ 11
0897A1- 122- US 2/ 96- 2/ 96	A double- blind, placebo controlled, randomized, crossover study of the effects of nighttime Fruncillo administration of zaleplon (10 mg and and 20 mg), zolpidem (10 mg and 20 mg), and triazolam (0.25 mg) on memory, learning, and psychomotor performance in healthy subjects	Zal 10 mg (1X 10 mg), oral, SD Zal 20 mg (2 X 10 mg), oral, SD Zolpidem 10 mg, oral, SD Zolpidem 20 mg, oral, SD Triazolam 0.25 mg, oral, SD Placebo, oral, SD	24/ 24
0897A1- 123- US 1/ 96- 1/ 96	Phase I, open- label, randomized, 4-period crossover, bioequivalence study of the final commercial zaleplon capsule formulation (product of phase II/ III manufacturing site [Gosport] vs product of marketed product manufacturing site [AWPI])	Zal 10 mg (2 X 5 mg), oral, SD Zal 10 mg (2 X 5 mg), oral, SD Zal 10 mg (1 X 10 mg), oral, SD Zal 10 mg (1 X 10 mg), oral, SD	31/ 31
0897A1- 124- US 5/ 96- 9/ 96	Phase I, double- blind, parallel sleep lab study of 10 or 20 mg of zaleplon, 30 mg of flurazepam, or placebo to determine next morning residual effects in healthy subjects	Zal 10 mg, (1 X 10 mg), oral, QD X 2 consecutive days Zal 20 mg, (2 X 10 mg), oral, QD X 2 consecutive days Flurazepam 30 mg, oral, QD X 2 consecutive days Placebo, oral, QD X 2 consecutive days	93/ 93
0897A1- 125- US 4/ 95- 5/ 95	Phase I, open- label, randomized, 3-period crossover, dose proportionality study of 5, 10, and 20 mg of zaleplon	Zal 5 mg (1 X 5 mg), oral, SD Zal 10 mg (2 X 5 mg), oral, SD Zal 20 mg (4 X 5 mg), oral, SD	26/ 26
0897A1- 126- SW 2/ 95- 3/ 95	Phase I, double- blind, 3- period crossover, pharmacokinetic/ pharmacodynamic drug interaction study of zaleplon 20 mg with imipramine 75 mg in healthy adults	Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, SD Imipramine 75 mg, oral, SD Zal 20 mg (1 X 5 mg + 1 X 15 mg) + Imipramine 75 mg, oral, SD Placebo, oral, SD	12/ 12
0897A1- 127- US 11/ 95- 11/ 95	Phase I, randomized, open- label, 2-period crossover, drug interaction study of zaleplon 10 mg with cimetidine 800 mg	Zal 10 mg, oral, SD Cimetidine, 800 mg, + Zal 10 mg, oral, SD	16/ 16
0897A1- 128- FR 3/ 95- 4/ 95	Phase I, open- label, nonrandomized, MD, 2- period crossover, study of the effect of multiple oral doses of rifampicin on the pharmacokinetics of zaleplon in healthy adults	Zal 10 mg (2 X 5 mg), oral, QD X Study day 1 and 15 Rifampicin 600 mg, oral, QD X Study day 2 to 15	14/ 14
0897A1- 129- SP 4/ 95- 5/ 95	Phase I, open- label, randomized, 3-period crossover, drug interaction study between a single 10- mg dose of zaleplon and a single 600- mg dose of ibuprofen	Zal 10 mg, oral, SD Ibuprofen 600 mg, oral, SD Zal 10 mg + Ibuprofen 600 mg oral, SD	18/ 17
0897A1- 130- SP 11/ 94- 3/ 95	Phase I, open- label, study of the effect of zaleplon 10 mg on the pharmacokinetics and pharmacodynamics of digoxin 0.375 mg in healthy males	Zal 10 mg, oral, QD X Study days 9 to 15 Digoxin 0.375 mg, oral, QD X Study days 1 to 15	28 (outpatient phase); 20 (inpatient phase)/20

Table 5.1.1.1 Clinical Studies of Zaleplon			
Protocol No. Start/ Stop Date	**Study Design**	**Study Drug Dose, Route, Duration**	**Enrolled ITT / Safety**
0897A1- 131- SW 3/ 95- 4/ 95	Phase I, double- blind, randomized, SD, 3- period crossover, drug interaction study of 20- mg dose of zaleplon with 50- mg doses of thioridazine	Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, SD thioridazine 50 mg, oral, SD Zal 20 mg (1 X 5 mg + 1 X 15 mg) + thioridazine 50 mg oral, SD	12/ 12
0897A1- 133- GE 7/ 95- 8/ 96	Phase I, comparative, double- blind, placebo- controlled, 3- period crossover, two- night dose administration, sleep lab study to investigate the safety of zaleplon in patients with sleep apnea	Zal 10 mg, oral, QD X 2 consecutive nights Zolpidem 10 mg, oral, QD X 2 consecutive nights Placebo, oral, QD X 2 consecutive nights	19/ 19
0897A1- 134- NE 5/ 96- 12/ 96	Phase I, double- blind, 7- period crossover, study of the residual effects of zaleplon 10 and 20 mg compared with zopiclone 7.5 mg in evening and middle- of- the- night administration on driving ability and memory in healthy subjects	Zal 10 mg (1 X 10 mg), oral, SD Zal 20 mg (2 X 10 mg), oral, SD Zopiclone 7.5 mg, oral, SD	29/ 29
0897A1- 138- US 5/ 96- 5/ 96	Phase I, randomized, open- label, 3- period crossover study of the effect of diphenhydramine (50 mg) on the pharmacokinetics of zaleplon (10 mg) in healthy adults	Zal 10 mg, oral, SD Diphenhydramine 50 mg, oral, Zal 10 mg + Diphenhydramine 50 mg, oral, SD	18/ 18
0897A1- 139- SW 5/ 96- 7/ 96	Phase I, double- blind, placebo- controlled, 2- period crossover drug interaction study of zaleplon (20 mg) with paroxetine (20 mg)	Zal 20 mg (2 X 10 mg), oral, QD X Study day 8 and 9 Paroxetine 20 mg, QD x Study day 1 to 9 Placebo, QD x Study day 1 to 9	25/ 24
0897A1- 140- US 6/ 96- 11/ 96	Phase I, double- blind, placebo- controlled, 5- period crossover, pharmacodynamic/ pharmacokinetic study of the comparative effects of zaleplon (10 and 20 mg) and zolpidem, 10 mg and 20 mg, in healthy adults with quantified EEG	Zal 10 mg (1 X 10 mg), oral, SD Zal 20 mg (2 X 10 mg), oral, SD Zolpidem 10 mg, 20 mg, oral, SD Placebo, oral, SD	10/ 10
0897A1- 141- US 4/ 96- 4/ 96	Phase I, open- label, randomized 2- period crossover, bioequivalence study of the final 20- mg zaleplon commercial capsule formulation (product of phase II/ III manufacturing site [Gosport] vs product of marketed product manufacturing site [redacted]	Zal 20 mg (2 x 10 mg), oral, SD Zal 20 mg, (1 x 5 mg + 1 x 15 mg), oral, SD	32/ 32
0897A1- 142- US 6/ 96- 7/ 96	Phase I, open- label, single- dose study to compare the pharmacokinetic and safety profiles of 10- mg doses of zaleplon in healthy elderly subjects (> 75 years), with the profiles in healthy young subjects (18 to 45 years)	Zal 10 mg, oral, SD	24/ 24
0897A1- 143- US 9/ 96- 10/ 96	Phase I, double- blind, placebo- controlled, 6- period crossover study to evaluate the residual effects of zaleplon 10 mg versus zolpidem 10 mg at staggered time of nocturnal administration from 5 hours before awakening until 2 hours before awakening	Zal 10 mg, oral, SD Zolpidem 10 mg, oral, SD Placebo, oral, SD	36/ 36
0897A1- 201- US 7/ 91- 6/ 92	Phase II multicenter, double- blind, placebo- controlled, randomized, four- way crossover, safety, tolerability, and polysomnographic study comparing 10- mg and 40- mg doses of zaleplon, 0.25- mg of triazolam, and placebo in patients with primary insomnia	Zal 10 mg (2 X 5 mg), oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12 day washout period Zal 40 mg (2 X 5 mg + 2 X 15 mg), oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12 day washout period Triazolam 0.25 mg, oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12 day washout period Placebo, orally, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12 day washout period	50/ 50

Table 5.1.1.1 Clinical Studies of Zaleplon			
Protocol No. Start/ Stop Date	**Study Design**	**Study Drug Dose, Route, Duration**	**Enrolled ITT / Safety**
0897A1- 202- US 7/ 91- 5/ 92	Phase II multicenter, double- blind, placebo- controlled, randomized, four- way crossover, safety, tolerability, and polysomnographic study of 20- mg and 60- mg doses of zaleplon, 0.25 mg of triazolam and placebo in patients with primary insomnia	Zal 20 mg (4 X 5- mg), oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12- day washout period Zal 60 mg (4 X 15- mg), oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12- day washout period Triazolam, 0.25 mg, oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12- day washout period Placebo, oral, QD X 2 consecutive nights X treatment period, 4 treatment periods separated by 5- or 12- day washout period	43/ 43
0897A1- 203- US 4/ 93- 2/ 94	Phase II 14- day multicenter, double-blind, comparative, parallel- group, efficacy, safety, tolerability, outpatient, sleep laboratory study of 5 mg and 10 mg of zaleplon, 0.25 mg of triazolam, and placebo in patients with primary insomnia	Zal 5 mg, oral, QD X 14- days Zal 10 mg, (2 X 5 mg), oral, QD X 14- days Triazolam 0.25 mg, oral, QD X 14- days Placebo, oral, QD X 14- days	132/ 132
0897A1- 204- EU 11/ 93- 7/ 95	Phase II, 28- day, multicentre, double-blind, comparative, parallel- group, efficacy, safety, tolerance, outpatient and sleep laboratory study of 10 mg and 20 mg of zaleplon versus 10 mg of zolpidem versus placebo in patients with primary insomnia	Zal 10 mg (2 X 5 mg), oral, QD X 28- days Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, QD X 28- days Zolpidem 10 mg, oral, QD X 28- days Placebo, oral, QD X 28- days	131/ 131
0897A1- 205- EU/ CA 4/ 93- 7/ 94	Phase II, 5- day, multicenter, double-blind, parallel group, efficacy, safety, tolerability, out- patient and sleep laboratory study of 2, 5, 10, and 20 mg of zaleplon compared with placebo in patients with primary insomnia	Zal 2 mg (2 X 1 mg), oral, QD X 5- days Zal 5 mg, oral, QD X 5- days Zal 10 mg, (2 X 5 mg), oral, QD X 5- days Zal 20 mg, (1 X 5 mg + 1 X 15 mg), oral, QD X 5- days Placebo, oral, QD X 5- days	137/ 137
0897A1- 207- US 4/ 94- 8/ 95	A Phase II, multicenter, double- blind, four- way crossover, safety, tolerability, and polysomnographic study of 2, 5, and 10 mg of zaleplon compared with placebo in elderly patients with chronic insomnia	Zal 2 mg, (2 X 1 mg), oral, QD X 2 nights separated by 5- or 12 day washout period Zal 5 mg, oral, QD X 2 nights separated by 5- or 12 day washout period Zal 10 mg, (2 X 5 mg), oral, QD X 2 nights separated by 5- or 12 day washout period Placebo, oral, QD X 2 nights separated by 5- or 12 day washout period	54/ 54
0897A1- 208- US 3/ 96- 9/ 96	Phase II multicenter, randomized, double-blind, three- period crossover study to evaluate residual sedation following the administration of 10 mg of zaleplon, 30 mg of flurazepam, and placebo after a nocturnal awakening in patients with sleep maintenance insomnia	Zal 10 mg, oral, QD x 2 days Flurazepam 30 mg, oral, QD x 2 days Placebo, oral, QD x 2 days	30/ 30
0897A1- 209- GE 4/ 96- 9/ 96	Phase II, 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	Zal 5 mg, oral, QD X 2 days Zal 10 mg, oral, QD X 2 days Zopiclone 7.5 mg, oral, QD X 2 days Placebo, oral, QD X 2 days	28/ 28
0897A1- 210- US 2/ 96- 9/ 96	Phase II, multicenter, double- blind, placebo- controlled, randomized, parallel-group polysomnographic study of single doses of 5 mg and 10 mg of zaleplon in subjects with transient insomnia	Zal 5 mg, oral, QD X 1 day Zal 10 mg, oral, QD X 1 day Placebo, oral, QD X 1 day	268/ 267

Table 5.1.1.1 Clinical Studies of Zaleplon

Protocol No. Start/ Stop Date	Study Design	Study Drug Dose, Route, Duration	Enrolled ITT / Safety
0897A1- 301- US 7/ 94- 12/ 95	Phase III, 28- day, multicenter, randomized, double- blind, comparator- and placebo- controlled, parallel- group safety, tolerability, and efficacy study of 5, 10, and 20 mg of zaleplon, compared with 10 mg of zolpidem or placebo, in adult outpatients with insomnia	Zal 5 mg, oral, QD X 28- days Zal 10 mg (2 X 5 mg), oral, QD X 28- days Zal 20 mg (1X 5 mg + 1 X 15 mg), oral, QD X 28- days Zolpidem 10 mg, oral, QD X 28- days Placebo, oral, QD X 28- days	598/ 590
0897A1- 302- US, 301 extension, Ongoing j (D79- P17) 29874 94- 2/ 97 (Data cut- off date)	Phase III, open- label extension of study 301- US, for the assessment of the safety and tolerability of zaleplon 10 mg administered once- daily for a maximum of 12 months to adult outpatients with insomnia	Zal 10 mg (2 X 5 mg), oral, QD X 6 to 12 months	242/ 242
0897A1- 303- EU/ CA 6/ 94- 10/ 95	Phase III, 28- day, multicenter, double- blind, comparative and placebo- controlled, parallel group, safety, tolerance and efficacy study of 5, 10, and 20 mg of zaleplon compared with 10 mg of zolpidem or placebo in adult outpatients with insomnia	Zal 5 mg, oral, QD X 28- days Zal 10 mg, (2 X 5 mg), oral, QD X 28- days Zal 20 mg, (1 X 5 mg + 1X 15 mg), oral, QD X 28- days Zolpidem 10 mg, oral, QD X 28- days Placebo, oral, QD X 28- days	615/ 613
0897A1- 304- EU/ CA, 303 extension Jan 95- Feb 97	Phase III, open- label extension of study 303- EU/ CA, long- term, safety and tolerance study of 10 mg of zaleplon administered once daily up to a maximum of 12 months in adult outpatients with insomnia	Zal 10 mg (2 X 5 mg), oral, QD X up to 12 months	42/ 42
0897A1- 306- US, double- blind phase 12/ 94- 8/ 96	Phase III, multicenter, randomized, double- blind placebo- controlled, parallel- group, safety, tolerability, and efficacy study of 5 and 10 mg of zaleplon, and 5 mg of zolpidem in elderly outpatients with insomnia	Zal 5 mg, oral, QD X 14- days Zal 10 mg, oral, QD X 14- days Zolpidem 5 mg, oral, QD X 14- days Placebo, oral, QD X 14- days	551/ 549
0897A1- 306- US, extension, Ongoing 1/ 95- 2/ 97 (Data cut- off date)	Phase III, open- label extension of study 306- US, safety, tolerability and efficacy study of 5 and 10 mg of zaleplon in elderly outpatients with insomnia (6- 12 months)	Zal 5 mg, oral, QD X 6 to12 months, (starting dose)	316/ 316
0897A1- 307- US/ CA 9/ 95- 9/ 96	Phase III, multicenter, randomized, double- blind, placebo- controlled, parallel- group, safety, tolerability, and efficacy study of 10 and 20 mg of zaleplon in adult outpatients with insomnia	Zal 10 mg, oral, QD X 14- days Zal 20 mg, (2 X 10 mg), oral, QD X 14- days	641/ 637
0897A1- 308- EU, double- blind phase 6/ 95- 10/ 96	Phase III, 14- day, multicenter, randomized, double- blind, placebo- controlled, parallel- group, safety, tolerance, and efficacy study of 5 and 10 mg of zaleplon in elderly outpatients with insomnia	Zal 5 mg, oral, QD X 14- days Placebo, oral, QD X 14- ays	437/ 437
0897A1- 308- EU, extension, Ongoing 6/ 95- 2/ 97 (Data cut- off date)	Phase III, optional open- label 6 months extension of study 308- EU, safety and efficacy study of 5 and 10 mg of zaleplon in elderly outpatients with primary insomnia	Zal 5 mg, oral, QD X 6 months Zal 10 mg, oral, QD X 6 months	171/ 171
0897A1- 312- US/ CA, 307 extension, Ongoing 11/ 95- 2/ 97(Data cut- off date)	Phase III, open- label extension of study 307- US/ CA safety and tolerability study of 10 or 20 mg of zaleplon administered once daily, for a maximum of 360 days, in adult outpatients with insomnia	Zal 10 mg, oral, oral, QD X up to 360 days (starting dose) Zal 20 mg, (2 X 10 mg), oral, QD X up to 360 days, (maximum dose)	317/ 317