5.0 Description of Clinical Data Sources

5.1 Primary Development Program

A table describing and enumerating all of the studies performed in the development program of zaleplon for human use is in the appendix in table 5.1.1.1. The primary data cutoff date for information included in this integrated summary of safety was September 30, 1996.

The sponsor's analysis of safety is based on pooled data from the US, Canadian, and European studies (all studies excluding those performed in Japan). The sponsor excluded the Japanese data from the analysis of pooled data from other phase II and III studies for the following stated reasons:

- The Japanese group was a completely different ethnic and cultural group
- The Japanese study included patients with moderate and severe non-psychotic illnesses and psychosomatic complaints as well as insomnia
- None of the phase II Japanese studies were placebo controlled (there were no Japanese phase III studies)

Ethnic and cultural differences are not compelling reasons to consider this a different potential population of insomnia patients; however, the broader spectrum of illnesses and illness severity truly defines the Japanese studies as having a different patient make-up. The difference in design (lack of placebo control) also makes pooling the data inappropriate. Therefore, the sponsors final decision to not pool the Japanese data in statistical analyses in the integrated summary of safety is appropriate. The sponsor does include deaths, serious adverse events, and adverse dropouts from the Japanese studies.

Table 5.1.1.2 enumerates the numbers of patients exposed to single and multiple doses of zaleplon during the development program including the Japanese studies. The groupings of Phase II and III studies that the sponsor considered were based largely on study design and the length of the treatment period. The groups used in the analyses for the ISS are as follows:

- **Group A-** Very short- term (1 or 2 day), placebo- controlled, sleep- lab studies. Except for study 210, all studies in this group were cross-over studies. The data from these studies were not combined with the other double-blind studies (e.g., in Group D), because of the difficulty in interpreting safety data from patients who were exposed to multiple doses of zaleplon and to comparators in differing,

randomized orders. The comparator group in Group A includes patients exposed to triazolam 0.25 mg (90 patients) flurazepam 30 mg (29), and zopiclone 7.5 mg (28).

- **Group B-** Short- term (5 or 14 day), parallel- group, placebo- controlled studies. These studies had treatment periods of 5 or 14 days with parallel-group designs. This group of studies constituted a pool of studies with short-term treatment with zaleplon. The comparator group in Group B includes patients exposed to triazolam 0.25 mg (31 patients) and zolpidem 5 mg (111).
- **Group C-** Long-term (28 day), parallel-group, placebo-controlled studies. This group was primarily used in the analysis of dose- related trends in the frequency of study events because all studies in the group had the same treatment period (28 days). The results of the dose-related trend analysis from this group were less likely to be confounded by differences in the length of the treatment period than such analyses from Group B or D. The comparator group in Group C consists of 271 patients exposed to zolpidem 10 mg.
- **Group D-** Phase II/ III, parallel- group, placebo- controlled studies. This group consists of all the Phase II/ III, parallel- group, placebo- controlled studies except study 210, which was a single- dose study. Group D provided the largest population of patients who were treated in a double-blind fashion without the complications of the crossover studies in Group A. This group was the primary focus of the safety analyses from the Phase II/ III studies. The comparator group in Group D includes patients exposed to triazolam 0.25 mg (31 patients), zolpidem 5 mg (111), and zolpidem 10 mg (271).
- **Group E-** Comparator- controlled studies. This group contained all Phase II/ III studies in which an active comparator drug was used. The comparator group in Group E includes patients exposed to triazolam 0.25 mg (121 patients), flurazepam 30 mg (29), zopiclone 7.5 mg (28), zolpidem 5 mg (111), and zolpidem 10 mg (271). Both parallel- group and crossover studies are included.
- **Group F-** Extended-treatment, open-label studies. These studies were used to analyze the safety results from extended treatment with zaleplon. All patients had originally been in parallel- group, placebo-controlled studies. They were either continued on zaleplon or switched from a comparator or placebo to zaleplon.
- **Group G-** All Phase II/ III studies. This group was used to look at safety data from all patients treated with zaleplon in Phase II and III studies.

The subjects/ patients in Phase I/ clinical pharmacology studies were analyzed separately in the following groups.

- **Group H-** All healthy volunteers. This group was the primary grouping for Phase I studies. Most of the subjects in Phase I were healthy volunteers and the data from these individuals were pooled for analysis.
- **Group I-** Special Populations. This group consisted of impairment, renal impairment, chronic obstructive pulmonary disease (COPD), and sleep apnea. The studies in this group were designed to examine the effect of certain pre- existing conditions on the pharmacokinetics of zaleplon. These patients were pooled separately from the healthy volunteers because of their pre-existing medical conditions.
- **Group J-** Abuse Liability. The subjects in these studies all had a history of drug abuse.
- **Group L-** All Phase I. This group contained all subjects/ patients enrolled in Phase I/ clinical pharmacology studies.

Most of the discussion of safety in section 8 focuses on the results from Groups D and F, the Phase II/ III, parallel- group, placebo controlled studies and the extended treatment, open-label studies, respectively. For the purposes of evaluation of efficacy, studies 301, 303, 306, 307, and 308 (all phase III placebo controlled studies) are considered individually as the pivotal studies.

5.1.2 Demographics

Baseline and demographic characteristics of patients treated with zaleplon, placebo, and comparator are summarized for Groups D, F, and G in Tables 5.1.2.1, 5.1.2.2, and 5.1.2.3 in the appendix respectively. For Group D, data are presented by the treatment group to which patients were randomized. For Group F, data are pooled into an "any zaleplon" group. For Group G, the treatment groups are broadly categorized as "any zaleplon," "any comparator, " and placebo; patients may be counted in more than one group because of crossover study designs.

Slightly more than half of the patients in Groups D and F were female (approximately 60%), and between 30 and 64 years of age. However, more patients in Group D who received 5 mg of zaleplon were between 65 and 69 years of age than any other age group. This is because the 5 mg dose was used primarily in studies with elderly patients. In addition, the mean age for patients in group D was higher for the 5 mg dose than for the other doses of zaleplon, as well as for placebo and comparator drugs. Most of the patients in groups D, F, and G were white.

5.1.3 Extent of 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.

Table 5.1.3.1 enumerates the numbers of patients exposed to varying doses of zaleplon for varying amounts of time. The sponsor has exposed 2069 patients in placebo controlled parallel group studies (group D), 400 patients for up to 6 months (group F), 53 patients for up to one year (group F) and 31 patients for greater than one year. The total and six month exposure thresholds were met in the sponsors development program; however, the one year exposure is only half of what is recommended by the ICH. The sponsor continues to collect long-term open label safety data. Given that the one year exposure need not be placebo controlled, then the safety and efficacy review may appropriately proceed on the understanding that the sponsor provide additional, one year exposure, safety data in the safety update.

Table 5.1.3.1 NUMBER OF PATIENTS EXPOSED TO ZALEPLON PER STUDY INTERVAL BY DOSE : EXTENDED- TREATMENT, OPEN- LABEL STUDIES (GROUP F)

Study Interval	5 mg	10 mg	15 mg	20 mg	30 mg	40 mg	Any Dose
Day 1- 7	408	675	--	38	--	--	1088
Day 8- 14	374	537	--	185	1	1	1016
Day 15- 21	191	632	--	178	--	1	964
Day 22- 28	150	616	--	171	2	1	920
Day 29- 60	128	570	--	153	3	--	818
Day 61- 90	106	468	--	113	2	--	668
Day 91- 120	80	394	--	72	1	--	537
Day 121- 150	68	345	1	63	--	--	469
Day 151- 180	47	307	--	49	--	--	400
Day 181- 210	10	224	--	32	--	--	263
Day 211- 240	6	89	--	25	--	--	116
Day 241- 270	6	68	--	14	--	--	88
Day 271- 300	8	66	--	8	--	--	78
Day 301- 330	6	53	--	--	--	--	59
Day 331- 360	5	48	--	--	--	--	53
Day >360	1	30	--	--	--	--	31

5.2 Secondary Sources of Clinical Information
All of the studies performed by the sponsor are listed in table 5.1.1.1. There were no other studies performed. The databases of primary concern for determination of efficacy are the placebo controlled phase III studies (301, 303, 306, 307, and 308). The databases of primary concern for the evaluation of safety are group D (placebo controlled, parallel group, phase II and III studies) and group F (open label long term exposure studies). The Japanese studies, phase I studies, and other phase II studies not subsumed under group D are secondary sources of clinical information. Secondary sources of clinical information were reviewed qualitatively for deaths, serious adverse events, and adverse dropouts.

5.2.2 Post Marketing Experience
Zaleplon has not been marketed in any country thus far; this is the initial NDA.

5.2.3 Literature
The literature search for the zaleplon (CL 284,846) NDA was performed in the following databases:

MEDLINE (1966- January 1997)
EMBASE (1988- December 1996)
BIOSIS (1992- December 1996)
Wyeth Ayerst Product Literature (covers W- A products from 1942 - February 1997 - 97022)

The sponsors warranted that they reviewed these databases and reported any potentially clinically significant adverse events that they found. No significant adverse events were found that were not addressed in section 8 since the only human exposure to zaleplon has been via the sponsor's development program.

5.3 Adequacy of Clinical Experience
See section 8.2
5.4 Data Quality and Completeness
See section 8.2

6.0 Human pharmacokinetic considerations

In healthy subjects, the pharmacokinetic profile of zaleplon has been examined after single doses up to 60 mg and multiple doses up to 30 mg administered daily for up to 10 days. Plasma concentrations of zaleplon increased in a linear dose-proportional manner over the entire dose range. Zaleplon was rapidly absorbed (t_{max} is approximately equal to 1 hour) and eliminated ($t_{½}$ is approximately equal to 1 hour), and showed no time dependent changes in pharmacokinetic profile or no signs of accumulation after multiple- dose administration of up to 30 mg per day. The pharmacokinetic profile of zaleplon in elderly subjects (>65 years), including those over 75 years of age, was not significantly different from that in younger subjects.

Bioequivalence has been demonstrated between the commercial capsules and experimental capsules used in the clinical trials. A food- effect study showed that a high- fat meal eaten just before taking zaleplon prolongs the absorption of the drug.

Zaleplon did not affect the pharmacokinetic or pharmacodynamic profiles of digoxin and warfarin. No pharmacokinetic interaction was observed with any of the central nervous system (CNS) active drugs that were tested (ethanol, imipramine, thioridazine, and paroxetine). However, imipramine, and thioridazine had an additive effect on decreased alertness and impaired psychomotor performance when coadministered with zaleplon. Ethanol and zaleplon potentiated each other's effects on reaction time, balance, and psychomotor performance for up to 4 hours after coadministration. Drugs that alter the biotransformation of zaleplon by enzyme induction (rifampicin) or inhibition (cimetidine) affected the plasma concentrations of zaleplon. In contrast, drugs that might affect renal drug excretion (ibuprofen) had no effect on zaleplon plasma concentrations.

Cimetidine inhibits both aldehyde oxidase (in vitro) and CYP3A4 (in vitro and in vivo), the primary and secondary enzymes, respectively, responsible for zaleplon metabolism. Concomitant administration of zaleplon (10 mg) and cimetidine (800 mg) produced an 85% increase in the mean C_{max} and AUC of zaleplon. However, based on the safety profile of zaleplon at twice the recommended dose and its short half- life, adjustment of the dose should not be necessary during concurrent administration of cimetidine. Diphenhydramine, an aldehyde oxidase inhibitor, does not change the pharmacokinetic profile of zaleplon when the two drugs are coadminitered. Studies of zaleplon with selective CYP450 3A4 inhibitors have not been performed. Rifampin, a 3A4

inducer, reduced the zaleplon Cmax by approximately 80%

The pharmacokinetics of zaleplon were not altered in patients with renal insufficiency. In patients with hepatic impairment, however, zaleplon clearance was markedly reduced from that in healthy subjects. This reduction in clearance caused an increase in mean peak concentration (C_{max}) and mean area under the plasma-concentration curve (AUC) of up to fourfold in patients with compensated hepatic impairment and up to sevenfold in patients with decompensated impairment.

Zaleplon is not highly bound to plasma proteins (fraction bound = 60%± 15%); therefore, the disposition of zaleplon is not expected to be sensitive to alterations in protein binding.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The sponsor presents 5 phase III, placebo controlled, studies in support of zaleplon as effective in the treatment of primary insomnia. All studies were multi center, randomized, double blind, fixed dose, and parallel group by design. Three studies examined the safety and efficacy of zaleplon in non elderly adults (301, 303, and 307) and two studies examined elderly adults (306 and 308). There were no pediatric efficacy studies performed.

Study 301 was a 28 day, US centered study of non-elderly adults using zolpidem as an active comparator. Study 303 was a 28 day non-US centered study of non-elderly adults in which zolpidem was used as an active comparator. Study 307 was a 14 day, U.S. centered study of non-elderly adults without an active comparator. Study 306 was a 14 day, US centered study with an active control (zolpidem), of elderly adults; this study included an optional 6 month open-label uncontrolled extension phase. Study 308 was a 14 day, non-US centered study without an active comparator of elderly adults; this study also included an optional 6 month open-label uncontrolled extension phase.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study 301

STUDY TITLE: A PHASE III, 28-DAY, MULTI CENTER, 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 (Protocol 0897A1-301-US; formerly American Cyanamid DP79-14; GMR-29874)

Study 301 was a 28 day, US centered, multi center, randomized, double blind, fixed dose (5, 10, and 20 mg), placebo and active controlled (zolpidem 10 mg), parallel group study of non-elderly adults with symptoms most consistent with either DSM-IV primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders.

Investigators and locations

Twenty-seven centers enrolled patients under this protocol. A list of investigators may be found in the appendix in table 7.2.1.1.

Objectives

1) To compare the 28-day safety, tolerability and efficacy of three fixed doses of zaleplon (5,10, 20 mg) with those of 10 mg of zolpidem or placebo in patients with insomnia. 2) To investigate any occurrence of daytime anxiety, pharmacologic tolerance during treatment, and rebound insomnia or withdrawal symptoms associated with discontinuation of treatment.

Study population
Men or nonpregnant women 18 to 65 years of age with a diagnosis of either primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders (patients were excluded if taking any psychotropic within 1-3 weeks of placebo run-in phase), who had a clinically normal physical, neurologic, and laboratory profile with no acute, chronic, or recurrent conditions that might affect the study.

Design
Study 301 is a 28 day, multi center, randomized, double blind, fixed dose (5, 10, and 20 mg), placebo and active controlled (zolpidem 10 mg), parallel group study. It consists of three phases after screening: 1) placebo run-in of one week; 2) 28 day double blind treatment phase; 3) 1 week placebo run-out phase. Each potentially eligible patient who had a documented history of either primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM- III- R), had first to discontinue all CNS medication and complete a prestudy washout period of 1 to 3 weeks (depending on the half-life of the medication). This washout period was not required for patients who had not taken any CNS medication within 1 to 3 weeks of initial screening. The date of initial interview and details of any CNS medication taken within the last month is recorded on the case report form (CRF).

During the placebo run-in phase, patients were given single-blind placebo medication and instructed to take one dose for 7 consecutive nights (night -7 through night -1)immediately before going to bed. The aim of the single-blind placebo run- in phase was to confirm patient eligibility and to obtain baseline data. These data were captured by using daily pre- and post sleep questionnaires. A patient who met all eligibility criteria on completion of the placebo run-in phase was randomly assigned to receive one of the five double-blind treatments for 28 nights.

Eligible patients were randomly assigned to one of the five treatment groups and given a 1- week supply of double-blind study medication, a diary card, a profile of mood states (POMS)

questionnaire, a Tyrer Symptom Checklist, and a 1- week supply of pre sleep and postsleep questionnaires. Patients were instructed to return in 1 week with a completed diary card, with completed POMS and sleep questionnaires, and all unused study medication. During the 28 days of double- blind treatment, the patients made an entry into the diary card and completed the presleep questionnaire each evening immediately before taking the study medication and going to bed. The postsleep questionnaires were filled out each morning after dose administration. The POMS questionnaire was filled out at the end of the day, immediately before dose administration on nights 1, 8, 15, and 22. The Tyrer Symptom Checklist was completed by each patient within 1 hour of awakening following nights 14, 26,27, and 28.

During the day before night +1, vital signs were assessed, and samples were collected for clinical laboratory studies (hematology, chemistry, urinalysis). The POMS questionnaire was given to the patient to be completed at home before dose administration on night +1.Three Tyrer Symptom Checklists were given to the patient for completion at home the morning following dose administration on nights +1,+ 2, and +3. The patients also received a 3- day supply of single-blind placebo, a diary card, and a 1- week supply of presleep and postsleep questionnaires. The patient was instructed to take the blinded study medication for 3 nights only, and to return in 7 to 10 days with a completed diary, completed sleep and POMS questionnaires, Tyrer Symptom Checklist, and all unused study medication. During the evenings of nights +4, +5, +6, and +7, the patients were instructed not to take any psychotropic medication, to complete the diary, the presleep questionnaire, and then to go immediately to bed.

Each patient was instructed to report for a follow-up visit within 3 days of night +7. During the follow- up visit, a physical examination, a neurologic assessment, and a 12- lead ECG were performed and vital signs recorded. Laboratory studies including hematology, chemistry, urinalysis, a urine drug screen, and serum β-HCG pregnancy test (if applicable).

Table 7.2.1.2 Dosing Schedule Study 301

Treatment	Placebo Run- in (Study Phase)	Double Blind (Study Phase)	Placebo Run- Out (Study Phase)
	Days -7 to -1	Days 1 to 28	Days +1 to +3
Placebo	2 x Placebo	2 x Placebo	2 x Placebo
Zaleplon 5 mg	2 x Placebo	1 x Placebo + 1 x 5 mg Zaleplon	2 x Placebo
Zaleplon 10 mg	2 x Placebo	2 x 5 mg Zaleplon	2 x Placebo
Zaleplon 20 mg	2 x Placebo	1 x 5 mg Zaleplon + 1 x 15 mg Zaleplon	2 x Placebo
Zolpidem 10 mg	2 x Placebo	1 x 10 mg Zolpidem + 1 x Placebo	2 x Placebo

Assessments

The primary efficacy variable was the patient's assessment of time to sleep onset (TSO) during week 1, obtained from the postsleep questionnaire. The secondary efficacy variables included TSO during weeks 2, 3, and 4, as well as total time slept (TTS), number of awakenings (NAW), and sleep quality during the 4 weeks of double-blind treatment. The Tyrer Symptom Checklist, POMS, and postsleep questionnaires were used during the study to investigate the potential withdrawal effects, daytime anxiety, rebound insomnia, and pharmacologic tolerance associated with zaleplon.

The schedule of safety and efficacy assessments are contained in the appendix in table 7.2.1.3.

Analysis Plan

The sponsor performed statistical analyses for two populations of patients-the intent to treat population (ITT) and the evaluable population. This review shall be limited to the ITT analyses as is the Division policy. The sponsor's definition of ITT is all patients who were randomly assigned to study medication, who received at least one dose of double-blind study drug, and for whom sleep questionnaires at baseline and during double-blind treatment were available for at least 1 night.

Baseline was defined as the mean of all single-blind placebo run-in nights; each weekly on-treatment value (summary week) was defined as the mean of all 7 nights of treatment for that week. These means were determined for each patient for each week and were used in all statistical analyses.

The primary efficacy variable was TSO (obtained from the patient post sleep questionnaires), and the primary endpoint was the week 1 comparison between the zaleplon treatment groups and the placebo group. Secondary endpoints for TSO were the comparisons between treatment groups during week 2 through week 4.

The three assumptions of the ANCOVA model (normality, homogeneity of variance, and parallelism) were tested to validate the use of this method of analysis. Because the tests indicated that the underlying assumptions of the ANCOVA model were not valid for the primary variable and for some secondary variables, appropriate non-parametric procedures were used. The nonparametric procedures paralleled those used in the parametric analysis but used rank-transformed data (covariate ranked separately from response variable) in the ANCOVA, and they produced pair wise comparisons by using Dunnett's and contrast F-tests. In these analysis, medians were the measure of primary concern.

Patient Disposition

830 patients entered the single-blind placebo run-in phase. 234 patients did not qualify to enter the double-blind treatment phase. Of the 595 patients randomly assigned to one of five double-blind treatments, 5 patients provided no data beyond baseline evaluations. The remaining 590 patients who were randomly assigned to receive study medication under double-blind conditions are included in all safety analyses. Four of the 590 patients had no valid baseline evaluations or no primary evaluations during therapy or within 24 hours of the last dose; therefore, they were excluded from the ITT analysis. The remaining 586 patients comprise the ITT efficacy population. Table 7.2.1.4 summarizes the disposition of patients in study 301.

7.2.1.4 Patient disposition Study 301				
	N total (%)	Zaleplon	Zolpidem	Placebo
Total Safety population	590	355	116	119
Total withdrawals	93 (16)	60 (17)	21 (18)	12 (10)
Adverse dropouts	29 (5)	18 (5)	7 (6)	4 (3)

Reasons leading to adverse dropout in this study shall be discussed in section 8. There was no statistical difference in the numbers of patients who dropped out among the treatment groups. Summary tables 7.2.1.5-10 list numbers of patients completed by time.

Baseline Demographics/Baseline severity of Illness
There were no statistically significant difference between groups with regard to baseline demographics such as age, sex, weight, ethnicity, primary diagnosis, number of awakenings (NAW), time to sleep onset (TSO), or total time slept (TTS).

Concomitant Medications
Patients were not allowed to take any psychotropic medications while participating in this study. The prohibited medications included sedative-hypnotics, antipsychotics, antidepressants, anxiolytics, anticonvulsants, lithium, other CNS depressants, or any other medications with CNS actions (especially over-the-counter sleeping aids, antihistamines, theophylline, corticosteroids, diet pills, and centrally acting β-adrenergic receptor blockers). Patients were advised not to consume alcohol. Among other drugs that were permitted, there was no disproportionate use between the groups.

Efficacy results
Nonparametric methods were used for the primary analyses because of indications that the assumptions for the normal theory analysis were violated. Nonparametric analyses were based on both the observed cases (OC) and the last observation carried forward data set to include the data for patients who prematurely dropped out.

Zaleplon 10 and 20 mg dose groups as well as the zolpidem 10 mg

group had statistically significantly shorter time to sleep onset (TSO) for both the OC and LOCF analysis [see tables 7.2.1.5 and 7.2.1.6] at week 1. In the OC analysis only did zaleplon 5 mg reach significance. TSO was the primary variable and the efficacy time point was 1 week. Zolpidem 10 mg was also superior to placebo at weeks 1 and 4 but not at weeks 2 and 3 with OC and LOCF analyses.

An examination of the secondary time points for the groups (weeks 2,3, and 4) is as follows. Zaleplon 20 mg was the only dose that remained significantly shorter than placebo throughout the study. The 10 mg dose was significantly shorter at weeks 1 and 3 but not at 2 and 4 in the OC analysis; likewise this group was significantly shorter at weeks 1, 3, and 4 in the LOCF analysis but not at week 2.

Zaleplon was not superior to placebo using the measure of total time slept (TTS) except at week one in the 20 mg group ($p=0.01$) with both OC and LOCF analyses. Zolpidem was superior to placebo in weeks 1-4 with both LOCF and OC analyses.

Number of awakenings (NAW) were significantly decreased with zaleplon in the 20 mg group during weeks 2 and 3 but not during weeks 1 and 4. Zolpidem 10 mg was effective at decreasing NAW during weeks 1 and 2 but not during weeks 3 and 4 [see tables 7.2.1.9-10].

Conclusions

Study 301 represents a positive study in the comparison of Zaleplon 10 mg and 20 mg to placebo. The 5 mg dose was not effective by any measure of hypnotic efficacy. Efficacy as measured by TSO endured for 28 days of the study with only the 20 mg dose. The 10 mg dose was unpredictably effective after the first week of the study.

7.2.2 study 303

Study Title: A Phase III, 28- Day, Multicentre, Double- Blind, Comparative, and Placebo- Controlled, Parallel- Group, Safety, Tolerance, and Efficacy Study of 5, 10, 20 mg of Zaleplon Compared with 10 mg of Zolpidem or Placebo in Adult Outpatients with Insomnia: Final Report 0897A1-303-EU/ CA GMR- 27310.

This is a 39 center fixed dose study in non-elderly adults.

Investigators and Sites

This study was performed in Europe and Canada. The investigators

and sites are listed in table 7.2.2.1 in the appendix.

Objectives
1) To compare the 28- day safety, tolerability and effectiveness of three fixed doses of zaleplon (5, 10, 20 mg) with those of 10 mg of zolpidem or placebo in patients with insomnia. 2) To investigate any occurrence of daytime anxiety or pharmacological tolerance during treatment, and rebound insomnia or withdrawal symptoms associated with discontinuation of treatment.

Study Population
The study population consisted of outpatients (18 to 65 years old) with a diagnosis of either primary insomnia or insomnia associated with mild non- psychotic psychiatric disorders based on subjective reporting of current history of insomnia, as defined by DSM- IIIR. During the preceding month complaints or symptoms of daytime impairments attributable to sleep disturbance and typical or modal time to sleep onset $\geq$ 30 minutes must have been present. In addition, patients should have exhibited prolonged ($\geq$ 30 minutes) or frequent nocturnal awakenings (three or more per night) with difficulty returning to sleep, or total sleep time $\geq$ 6.5 hours on average.

Design
This was a phase III, multicentre, randomised, double-blind, parallel-group, 28- day, zolpidem and placebo controlled, safety, tolerability and efficacy study of three doses of zaleplon in outpatients. Patients were screened and taken off all psychotropic medication for three weeks. Following screening was a 7- night single-blind placebo run-in phase. Eligible patients were then randomly allocated to one of the five treatment groups. Each patient was treated for a maximum of 28 days, after which the patient entered a 3-night placebo run- out phase.

Assessments
The primary efficacy variable was the patient's assessment of time to sleep onset (TSO) during week 1, obtained from the postsleep questionnaire. The secondary efficacy variables included TSO during weeks 2, 3, and 4, as well as total time slept (TTS), number of awakenings (NAW), and sleep quality during the 4 weeks of double-blind treatment. The Tyrer Symptom Checklist, POMS, and postsleep questionnaires were used during the study to investigate the potential withdrawal effects, daytime anxiety, rebound insomnia, and pharmacologic tolerance associated with zaleplon.

The schedule of safety and efficacy assessments are contained in

the appendix in table 7.2.2.2.

Analysis plan
The sponsor performed statistical analyses for two populations of patients-the intent to treat population (ITT) and the evaluable population. This review shall be limited to the ITT analyses as is the Division policy. The sponsor's definition of ITT is all patients who were randomly assigned to study medication, who received at least one dose of double-blind study drug, and for whom sleep questionnaires at baseline and during double-blind treatment were available for at least 1 night.

The primary efficacy variable was TSO in the intent-to-treat (ITT) population. The primary comparisons of interest were zaleplon 5 mg, zaleplon 10 mg and zaleplon 20 mg versus placebo for the primary efficacy variable during week 1 in an ITT observed cases analysis. All other comparisons and all other variables (TTS, NAW and sleep quality) we reconsidered secondary. Primary and secondary efficacy parameters were analyzed by ANCOVA analysis with treatment, center grouping as factors and the baseline value as a covariate. The treatment-by-center interaction was included in the model for the last observation carried forward (LOCF) case analyses for TSO, TTS and quality of sleep. Due to missing values, some adjusted means would have been non-estimable if this interaction had been included in the model for the other analyses. Therefore the interaction was not included in the ANCOVA model for the observed cases analysis of all variables or for LOCF cases analysis of NAW. Three assumptions of the ANCOVA model were tested to validate the use of this method of analysis: normality, homogeneity of variance and parallelism. A rank transformation was applied to TSO, TTS and NAW because the assumption of normality, parallelism of slopes, or both were rejected.

Patient Disposition
Six hundred fifteen (615) patients were randomly assigned to receive either zaleplon 5 mg, 10 mg, or 20 mg, zolpidem 10 mg, or placebo under double- blind condition. The patients were distributed among 39 investigators. Two patients from center 38 never took the double- blind medication . The remaining 613 patients were included in the safety analysis. Due to quality issues, center 30338 (37 patients) was excluded from the ITT population. In addition, 2 patients did not satisfy the ITT population criteria. The remaining 574 patients comprised the ITT population.

Table 7.2.2.3 summarizes the disposition of patients in study

303.

7.2.2.3 Patient disposition Study 303				
	N total (%)	Zaleplon	Zolpidem	Placebo
Total Safety population	613	365	122	126
Total withdrawals	80 (13)	48 (13)	19 (16)	13 (10)
Adverse dropouts	18 (3)	11 (3)	7(6)	1 (<1)

There were significantly greater adverse dropout groups in treatment groups as opposed to placebo. Reasons leading to adverse dropout in this study shall be discussed in section 8.

Baseline Demographics/Baseline severity of Illness
There were no statistically significant difference between groups with regard to baseline demographics such as age, sex, weight, ethnicity, primary diagnosis, number of awakenings (NAW), time to sleep onset (TSO), or total time slept (TTS).

Concomitant Medications
Patients were not allowed to take any psychotropic medications while participating in this study. The prohibited medications included sedative-hypnotics, antipsychotics, antidepressants, anxiolytics, anticonvulsants, lithium, other CNS depressants, or any other medications with CNS actions (especially over-the-counter sleeping aids, antihistamines, theophylline, corticosteroids, diet pills, and centrally acting β-adrenergic receptor blockers). Patients were advised not to consume alcohol. Among other drugs that were permitted, there was no disproportionate use between the groups on visual examination of descriptive data.

Efficacy Results
Nonparametric methods were used for the primary analyses because of indications that the assumptions for the normal theory analysis were violated. Nonparametric analyses were based on both the observed cases (OC) and the last observation carried forward data set to include the data for patients who prematurely dropped out.

Zaleplon patients taking 10 and 20 mg/day had significantly shorter TSO than placebo patients at weeks one through four on

both LOCF and OC analyses of the ITT population. Zolpidem also showed significantly short TSO in weeks 1-3 but not week 4 on both LOCF and OC analyses (see tables 7.2.2.4-5 in the appendix).

Secondary efficacy measures of TTS and NAW did not fair as well with zaleplon. Only the 20 mg/day dose significantly lengthened TTS in weeks 1,2, and 4 but not week 3 (on both the OC and LOCF analyses-tables 7.2.2.6-7), while zolpidem significantly lengthened TSS throughout the study's duration. NAW was not decreased by either zolpidem or zaleplon at any dose compared to placebo (tables 7.2.2.8-9).

Conclusions
Study 303 represents a positive study by the sponsor's protocol criteria. Zaleplon at doses of 10 and 20 mg/day were more effective than placebo at decreasing TSO. Though zaleplon was somewhat effective at increasing TTS at 20 mg/day, the results were not consistent across the study as they were for zolpidem. NAW was not significantly decreased by either zaleplon or zolpidem. Therefore, I conclude that zaleplon 10 mg is effective in shortening TSO but not at increasing TTS. Higher doses of zaleplon may increase TTS but the results are not consistently positive. No comment may be made regarding NAW since neither zolpidem nor zaleplon were better than placebo at decreasing NAW. The usual NAW is relatively small and necessitates that patients fall asleep after interrupted sleep in order to score higher NAW.

7.2.3 Study 306
Study Title: A PHASE III, 14- DAY, MULTI CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED, PARALLEL- GROUP, SAFETY, TOLERANCE, AND EFFICACY STUDY OF 5 AND 10 MG OF ZALEPLON IN ELDERLY OUTPATIENTS WITH INSOMNIA. This was a study of elderly (aged >65 years) outpatients with symptoms of primary insomnia or insomnia associated with non-psychotic psychiatric disorders.

Investigators and locations
This is a 50 site, multi center study performed in eight countries in western Europe (4 in Belgium, 16 in France, 7 in Germany, 4 in Italy, 1 in the Netherlands, 8 in Spain, 6 in Sweden and 4 in the United Kingdom). Principal investigators and their sites of study are listed in table 7.2.3.1 in the appendix.

Objectives
The specific objectives of study 306 were to compare the efficacy, safety, and tolerability of 5 or 10 mg of zaleplon with that of 5 mg of zolpidem or placebo as a hypnotic in elderly outpatients patients with a history of primary insomnia of at

least 3 month's duration.

Study Population
Patients in this study were volunteer men and women aged > 65 years with a diagnosis of primary insomnia (DSM-IV) for at least 3 months duration. Patients were not to have any other psychiatric diagnosis. Patients were to be otherwise healthy or, if on chronic medication (e.g. thyroid replacement) patients were to be on a stable dose of medicine and have a stable chronic medical condition.

Design
This was a phase III, multi center, randomized, double- blind, 14- day, placebo and comparator controlled, parallel group study, to investigate the safety and tolerability of two doses of zaleplon and its effectiveness as a hypnotic in outpatients. After a 7- day single- blind placebo run- in phase, eligible patients were randomly allocated to one of four treatment groups. The patients were treated for 14 days, after which they entered a 7 day single blind placebo run out phase. This was a fixed dose study without any up or down titration. Study groups were zaleplon 5 and 10 mg, zolpidem 5 mg, and placebo. After the 14 day double blind treatment phase there was a 7 day single blind placebo run-out phase. This phase was included to monitor potential withdrawal effects and rebound insomnia.

There also followed a 12 month, open label, extension phase which shall be considered for its contribution to the safety data base in section 8 of this review; however, this phase does not substantially contribute to the efficacy database.

Assessments
The primary efficacy variable was TSO. Secondary efficacy variables included TTS and NAW. These efficacy variables were obtained from post-sleep questionnaires. Safety assessments were based on reports of study events and the results of routine physical examinations, laboratory determinations, vital signs, and ECGs. The routine physical examinations included the recording of sitting blood pressure, body temperature, and pulse rate. ECGs were never performed when patients were on drug in this study; however, clinical labs were performed at screening, after washout, on the last day of double blind treatment, and at follow up. (See table 7.2.3.2 in the appendix).

Analysis Plan
The sponsor performed statistical analyses for two populations of patients-the intent to treat population (ITT) and the evaluable

population. This review shall be limited to the ITT analyses as is the Division policy. The sponsor's definition of ITT is all patients who were randomly assigned to study medication, who received at least one dose of double-blind study drug, and for whom sleep questionnaires at baseline and during double-blind treatment were available for at least 1 night.

The primary efficacy variable was TSO. Baseline was defined as the mean of single-blind placebo run-in nights -7 through -1; week 1 was defined as the mean of treatment nights 1 through 7, week 2 was defined as the mean of treatment nights 8 through 14.

Primary and secondary efficacy variables were analyzed by analysis of covariance (ANCOVA) with treatment, center, and their interaction as factors, and baseline value as a covariate. The following three assumptions of the ANCOVA model were tested to validate the use of this method of analysis: normality, homogeneity of variance, and parallelism. Because the assumptions of normality were not satisfied, an ANCOVA was performed on ranked data (nonparametric). Analyses of the interaction of treatment and center were virtually always statistically nonsignificant. This means that the effects of zaleplon (or zolpidem, or placebo) were consistent across centers. As a result, data from all centers were pooled for the analyses presented in this study and did not include an interaction term in the ANCOVA. For nonparametric analyses, the ANCOVA was performed on ranked data.

Patient Disposition

A total of 1,224 patients entered the initial screening phase. Five hundred and fifty-one (551) of these 1,224 patients completed the placebo- run- in phase and were randomly assigned to one of the four treatment groups. Two patients randomly assigned to the zaleplon 5 mg treatment group did not provide any data after baseline, and were not included in the ITT population. This left 549 patients in the ITT population for study 306. Table 7.2.3.3 reflects the numbers of patients dropping out for any reason and for adverse events.

Table 7.2.3.3 Patient disposition Study 306 n (%)				
Group	**Placebo**	**Zaleplon 5 mg**	**Zaleplon 10 mg**	**Zolpidem 5 mg**
Intent- to-treat	107	166	165	111
Total dropouts	12 (11)	18 (11)	16 (10)	7 (6)
Adverse Dropouts	7 (7)	9 (5)	7 (4)	5 (5)

Reasons leading to adverse dropout in this study shall be discussed in section 8.

Baseline Demographics/Severity of Illness
There were no group differences in age, weight, depression or anxiety scale scores, sex, or ethnic origin. There was a fairly large difference in TSO between groups at baseline.

Table 7.2.3.4 Baseline TSO (minutes) in ITT patients					
Study Period	**Values**	**Placebo**	**Zaleplon 5 mg**	**Zaleplon 10 mg**	**Zolpidem 5 mg**
Days -7 to -1	n	107	165	164	111
	Median	68.57	76.67	64.75	59.17
	Mean	78.30	86.44	77.82	80.06
	SD	42.64	52.70	47.29	55.49
	Minimum	24.00	21.67	22.14	23.57
	Maximum	201.43	328.00	300.00	338.57

The sponsor did not report p-values for group baseline differences for severity of insomnia; however, these differences are fairly large and probably significant. The sponsor did not report p-values for baseline group differences for the efficacy variables TTS or NAW; however, these numerical difference appear smaller and probably insignificant.

Concomitant Medications
Patients were not allowed to take any psychotropic medications while participating in this study. The prohibited medications included sedative-hypnotics, antipsychotics, antidepressants, anxiolytics, anticonvulsants, lithium, other CNS depressants, or any other medications with CNS actions (especially over-the-counter sleeping aids, antihistamines, theophylline, corticosteroids, diet pills, and centrally acting β-adrenergic receptor blockers). Patients were advised not to consume

alcohol. The sponsor did not report p-values for between group differences in the use of concomitant medication but did report descriptive statistics. There appeared to be no significant difference between groups with respect to specific types of concomitant medications except for anilides (e.g. acetaminophen) (placebo=18%; zaleplon 5 mg=22%; zaleplon 10 mg=15%; zolpidem 5 mg=8%).

Efficacy Results

Nonparametric methods were used for the primary analyses because of indications that the assumptions for the normal theory analysis were violated. Nonparametric analyses were based on the observed cases (OC) data set only.

TSO was significantly less for zaleplon 10 mg than for placebo at week one and two. The TSO for zaleplon 5 mg at week one was not significantly different than for that of the placebo group. The TSO for zolpidem 5 mg was significantly less than the TSO for the placebo group at both week one and two (see table 7.2.3.5 in the appendix).

TTS was significantly longer at weeks one and two for the zolpidem treatment group. TTS for zaleplon 5 mg was not distinguishable from the placebo group at weeks one and two. TSO for zaleplon 10 mg was significantly longer than placebo at week one(median difference of 38 minutes p=0.02) but not at the two. week point (see table 7.2.3.6 in the appendix).

NAW was not different from placebo for zaleplon at any dose or time yet was significantly less for zolpidem 5 mg at both weeks one and two (see table 7.2.3.7 in the appendix).

Conclusions

This represents a positive study for zaleplon 10 mg but not 5 mg. The half life of zaleplon is such that it is not surprising that the TTS or NAW are different than placebo, yet it is effective at decreasing the TSO. The sponsor did not present LOCF data for this study even though this analysis was requested prior to the submission of the NDA; however, the dropout rate was low enough that it is unlikely that there would be a great difference (if any) between the OC and LOCF analyses.

7.2.4 Study 307

Study Title: A Phase III, Multi center, Randomized, Double Blind, Placebo Controlled, Parallel Group, Safety, Tolerability, and Efficacy Study of 10 and 20 mg of Zaleplon in Adult Outpatients with Insomnia.

This was a multi center, US and Canadian based study of non-elderly (aged 18-65 years) adults with primary insomnia or insomnia associated with non-psychotic psychiatric disorders.

Investigators and sites
This is a 39 site, multi center study performed in the US (32 centers) and (7 centers) Canada. Principal investigators and their sites of study are listed in table 7.2.4.1 in the appendix.

Objectives
The objectives of this study were to compare, during week 1 of a two week double blind treatment period, the safety, tolerability and hypnotic efficacy of 10 mg of zaleplon and placebo in outpatients with a history of insomnia. 2) To investigate, during week 2, the safety, tolerability, and hypnotic efficacy of 10 or 20 mg of zaleplon compared with those of placebo. 3) To investigate effects historically associated with hypnotics, such as rebound insomnia or withdrawal symptoms occurring during the single blind placebo run out phase.

Study Population
Men or nonpregnant women 18 to 65 years of age with a diagnosis of either primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders, who had a clinically normal physical, neurologic, and laboratory profile with no acute, chronic, or recurrent conditions that might affect the study.

Design
Study 307 was a multi center, randomized, double blind, placebo controlled, parallel group, fixed dose, combination one week and two week study. Patients were randomized at the beginning of the study to either zaleplon 10 mg, zaleplon 20 mg or placebo groups; however, during week one all patients who were randomized to any zaleplon group take 10 mg at bedtime. During the second week patients in the designated 20 mg group had their dose of zaleplon increased from 10 mg to 20 mg at bedtime. The 14 day double blind phase was preceded by a 7 day single blind placebo run in phase and was followed by a 7 day single blind placebo run out phase. The 7 day placebo run in phase was preceded by a period of up to 21 days drug washout period for patients who were on psychotropic drugs at screening.

Assessments
The primary efficacy variable was TSO at the end of week one. Secondary efficacy variables included TTS and NAW and TSO at the end of week two. These efficacy variables were obtained from post-sleep questionnaires. Safety assessments were based on

reports of study events and the results of routine physical examinations, laboratory determinations, vital signs, and ECGs. The routine physical examinations included the recording of sitting blood pressure, body temperature, and pulse rate. ECGs were never performed when patients were on drug in this study; however, clinical labs were performed at screening, after washout, and at follow up. The Zung Depression and Anxiety Scales were performed only once at screening.

Analysis Plan

The primary analysis of interest was performed on the intent- to-treat population. The primary efficacy parameter was the patients' assessment of TSO at double blind weeks 1. Comparisons were made at week 1 between zaleplon and placebo, when the zaleplon group consisted of all patients assigned to the 10 mg/ 10 mg or 10 mg/ 20 mg zaleplon groups (patients in both groups took 10 mg zaleplon in week 1). Comparisons at week 2 were between zaleplon 10 mg and placebo, and zaleplon 20 mg and placebo, using Dunnett's test for multiple comparisons.

Baseline was defined as a mean of single blind, placebo run in nights -7 through -1; week 1 consists of days on medication from the double blind week 1 medication pack, and week 2 consists of days on medication from the double blind week 2 medication pack.

Analysis of the primary efficacy variables was performed by using analysis of covariance (ANCOVA) with treatment, center and treatment by center interaction as factors in the model, and baseline as a covariate. If the assumptions of normality, parallelism, or homogeneity of variance were violated, then a rank transformation was applied to the data, and the ranks were analyzed by using the ANCOVA. In all ANCOVA models, if a treatment by center interaction was found to be statistically significant ($p \leq 0.05$), an assessment of the magnitude and direction was to be made.

Patient Disposition

1,158 were initially screened. Of those 869 entered the placebo run- in phase. 641 patients who completed the placebo run- in phase and met the eligibility criteria were randomly assigned to receive either 10 mg of zaleplon or placebo for 2 weeks or zaleplon 10 mg for 1 week followed by zaleplon 20 mg for a second week. Four patients received double blind study drug but never returned to follow up. Therefore 638 patients comprised the ITT population of study 307. Table 7.2.4.2 displays the disposition of those patients.

Table 7.2.4.2 Patient disposition Study 307 n (%)			
Group	**Placebo**	**Zaleplon 10 mg**	**Zaleplon 10-20 mg**
Intent- to-treat	153	242	242
Total dropouts	13 (8)	18 (7)	19 (8)
Adverse Dropouts	3 (2)	5 (2)	6 (2)

Descriptive statistics of the above groups reveal no difference in the overall or adverse dropout rate among the three groups. Reasons leading to adverse dropout in this study shall be discussed in section 8.

Baseline Demographics/Severity of Illness
There were no group differences in age, weight, Zung depression or anxiety scale scores, TSO, TTS, NAW, sex, or ethnic origin.

Concomitant Medications
Patients were not allowed to take any psychotropic medications while participating in this study. The prohibited medications included sedative-hypnotics, antipsychotics, antidepressants, anxiolytics, anticonvulsants, lithium, other CNS depressants, or any other medications with CNS actions (especially over-the-counter sleeping aids, antihistamines, theophylline, corticosteroids, diet pills, and centrally acting β-adrenergic receptor blockers). Patients were advised not to consume alcohol. The sponsor did not report p-values for between group differences in the use of concomitant medication but did report descriptive statistics. There appeared to be no significant difference between groups with respect to specific types of concomitant medications.

Efficacy Results
Nonparametric methods were used for the primary analyses because of indications that the assumptions for the normal theory analysis were violated. Nonparametric analyses were based on the observed cases (OC) data set only.

TSO was significantly shorter for zaleplon treated patients (all at 10 mg/day) versus placebo at week one and for both the 10 and 20 mg groups at week two(see table 7.2.4.3. in the appendix).

TTS was significantly lengthened for zaleplon patients at both weeks one and two at both 10 and 20 mg doses. (See table 7.2.4.4 in the appendix).

NAW for zaleplon was not significantly different than placebo at all time points and doses. (See table 7.2.4.5 in the appendix).

Conclusions

Study 307 supports the hypothesis that zaleplon decreases time to sleep onset. This was the sponsor's primary variable. At week one the median difference between zaleplon and placebo patients was only 8.6 minutes; however, other studies in this submission show more clinically significant decreases in TSO. The TSO at week two is more clinically significant in that TSO is roughly 20 and 25 minutes shorter in the 10 and 20 mg zaleplon groups respectively than in placebo.

The median time slept (TTS) was only 7 minutes longer than the placebo group at week one (all on 10 mg) and 7 and 12 minutes longer for the 10 and 20 mg groups respectively. Other studies in this submission do not see significant changes in TTS but have smaller numbers of subjects. These small changes become statistically significant because the study is highly powered.

7.2.5 Study 308

Study Title: A PHASE III, 14- DAY, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, SAFETY, TOLERANCE, AND EFFICACY STUDY OF 5 AND 10 MG OF ZALEPLON IN ELDERLY OUTPATIENTS WITH INSOMNIA.

This is a 14 day European study of patients with primary insomnia or insomnia associated with a non-psychotic mental illness.

Investigators and sites

This was a 50 center study that was performed in western Europe. There were 4 sites in Belgium, 16 in France, 7 in Germany, 4 in Italy, 1 in the Netherlands, 8 in Spain, 6 in Sweden and 4 in the United Kingdom. The investigators, their addresses and the number of patients at each may be found in the appendix in table 7.2.5.1.

Objectives

The objectives of this study were to compare the efficacy, safety and tolerability during 14 days of treatment with 5 mg and 10 mg of zaleplon and placebo in elderly outpatients with a history of primary insomnia for at least the past 3 months b) To investigate, after 14 days of double blind therapy and after 6 months of open label therapy, any occurrence of rebound insomnia associated with zaleplon.

Study Population

Patients consisted of otherwise healthy men and women aged $\geq$ 65 years who had a diagnosis of primary insomnia based on subjective reporting of a history of sleep disturbance for at least the prior 3 months, had no history of any major psychiatric disorder or significant CNS organic disorders, and had sleep-associated daytime complaints. In characterizing their sleep problem, reported sleep latency of 30 minutes or more, and either frequent nocturnal awakenings (three or more per night) or a total sleep time of 6.5 hours or less.

Design

This was a phase III, multi center, randomized, double blind, 14 day placebo controlled, parallel group, efficacy, safety, and tolerability study of 2 doses of zaleplon in outpatients. Following a 7 night single blind placebo run- in phase, eligible patients were randomly allocated to one of 3 treatment groups (placebo, zaleplon 5 mg/day and zaleplon 10 mg/day). Each patient was treated for 14 days, after which he or she entered a 7 night single blind placebo run out phase.

After the completion of the double blind treatment phase patients had the option to continue on to an open label treatment phase of six months duration. Data from the open label phase is pertinent to safety and shall be discussed in section 8.

Assessments

The primary efficacy assessment was the TSO as measured by sleep questionnaire. Secondary efficacy assessments included TTS. and NAW. Safety assessments included screening psychiatric and medical history, Zung Depression and Anxiety Scales physical exam ECG, clinical chemistry, hematology, urinalysis, and urine drug screen. The clinical laboratory studies were performed at screening, during double blind study drug administration and at the end of the 7 day placebo washout period. The ECG was only performed at screening and at the end of the placebo washout. There is no ECG data from this study where patients are on drug. The Zung Depression and Anxiety Scales were performed only at screening. (See table 7.2.5.2 Schedule of assessments for study 308 in the appendix).

Analysis Plan

The primary analysis of interest was performed on the intent- to-treat population. The primary efficacy parameter was the patients' assessment of TSO. The statistical analysis was based on the pooled data from the individual study sites. Baseline was defined as a mean of single blind, placebo run in nights -7 through -1; week 1 consists of days on medication from the double blind week 1 medication pack, and week 2 consists of days on medication from the double blind week 2 medication pack.

Analysis of the primary efficacy variables was performed by using analysis of covariance (ANCOVA) with treatment, center and treatment by center interaction as factors in the model, and baseline as a covariate. Since the assumptions of normality, parallelism, and homogeneity of variance were violated, a rank transformation was applied to the data, and the ranks were analyzed by using the ANCOVA.

Patient Disposition

609 patients were screened and 437 met entrance criteria and were randomized to either placebo, zaleplon 5 mg, or zaleplon 10 mg/day groups. 11 patients were dropped from study site 30825 due to non-adherence to a blind-quality check. Four more patients were dropped as they did not have adequate baseline data. This left 422 patients who entered the double blind treatment phase and comprised the ITT population. 405 patients completed double blind treatment.

Baseline Demographics/Severity of Illness
There were no group differences in age, weight, Zung depression or anxiety scale scores, sex, or ethnic origin. TSO, TTS, and NAW were not statistically tested for groups differences at baseline; however, visual inspection of the descriptive median baseline TSO, TTS, and NAW revealed no large intergroup differences in these values. (See efficacy tables 7.2.5.4-7 in the appendix).

Concomitant Medications
Patients were not allowed to take any psychotropic medications while participating in this study. The prohibited medications included sedative-hypnotics, antipsychotics, antidepressants, anxiolytics, anticonvulsants, lithium, other CNS depressants, or any other medications with CNS actions (especially over-the-counter sleeping aids, antihistamines, theophylline, corticosteroids, diet pills, and centrally acting β-adrenergic receptor blockers). Patients were advised not to consume alcohol. The sponsor did not report p-values for between group differences in the use of concomitant medication but did report descriptive statistics. There appeared to be no significant difference between groups with respect to specific types of concomitant medications.

Efficacy Results
Nonparametric methods were used for the primary analyses because of indications that the assumptions for the normal theory analysis were violated. Nonparametric analyses were based on the observed cases (OC) and LOCF data sets for the primary efficacy variable TSO but only OC analysis was performed for the secondary variables TTS and NAW.

TSO was significantly shorter than placebo in both the OC and LOCF analysis at both week one and week two (see table 7.2.5.4.and 7.2.5.5).

TTS marginally met criteria for significance (p=0.04) for zaleplon at 10 mg/day at the end of week one in the OC analysis. At week two there was no significant improvement in TTS at any dose(See table 7.2.5.6). No LOCF analysis was performed.

NAW were actually significantly fewer than the zaleplon 10 mg group at week one. There was otherwise no significant difference between placebo and zaleplon (see table 7.2.5.7).

Conclusion

Study 308 represents another study supporting the efficacy of zaleplon with respect to decreasing TSO. TTS was only marginally different than placebo. Placebo faired nearly better than zaleplon with respect to NAW; however, the sponsor neglected to examine group differences at baseline. NAW was numerically greater in the zaleplon groups at baseline in study 308. Whether significantly so or not is unknown; however, even if the placebo group had significantly fewer NAW at baseline, it would not argue strongly against the aggregate data that shows that zaleplon has little or no effect on NAW when measure with sleep questionnaires.

7.2.6 Other studies mentioned in labeling supporting additional indications-Treatment of transient insomnia

Two trials using different models of transient insomnia were conducted with healthy subjects in sleep laboratories. Study 209- GE was a 2- day 4- period crossover study to model time zone or work cycle shift. On the first of the 2 nights, the subjects adapted to the recording session and went to sleep at their usual time, and on the second of the 2 nights, they were instructed to go to sleep 4 hours earlier than on the first night. Study 210-US was a 1- night parallel- group study to model transient insomnia because subjects frequently show impaired sleep on the first night in a novel environment such as the sleep laboratory.

7.2.6.1 Study 210 A 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

Investigators and sites

Investigators, the sites at which patients were studies, and the numbers of patients at each site may be found in the appendix in table 7.2.6.1.1.

Objectives

In this study, polysomnography (PSG) and sleep questionnaire data were used to evaluate the hypnotic efficacy and safety of single doses of 5 mg and 10 mg of zaleplon and placebo in subjects with transient insomnia in a sleep laboratory (first night effect).

Study Population

Subjects in this study were healthy men and women, aged 26-60 years who were normal sleepers who completed a sleep diary for seven days prior to entering the sleep lab. 269 subjects enrolled. 264 subjects comprised the ITT population.