CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020859

STATISTICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

Addendum to NDA review: review of additional phase II studies pertinent to combined efficacy and safety issues- studies 201, 202, 203, 204, 205, and 207.

Application Information

NDA #:	20-859
Sponsor:	Wyeth Ayerst
Clock Date:	December 31, 1997

Drug Name

Generic Name:	Zaleplon
Trade Name:	Sonata

Drug Categorization

Pharmacological Class:	Pyrazolopyrimidine
Proposed Indication:	Treatment of insomnia (hypnotic)
NDA Classification:	1 S
Dosage Forms:	5 and 10 mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewer:	Paul J. Andreason, M.D.

Summary

Zaleplon is a new chemical entity that is ,currently under review for use as a hypnotic at a recommended dose of 10 mg for adults , 65 years old and 5 mg for patients over the age of 65 years. The sponsor refers to several studies in labeling that are pertinent to specific marketing claims that were not covered in the original NDA review. The following addendum reviews these studies for efficacy.

The sponsor sites study 204 as evidence that zaleplon does not increase the numbers of awakenings (NAW) in the latter quarter of the night; however, review of this study for efficacy shall show that it did not show any improvement in latency to persistent sleep (LPS) over placebo except on the first night of the study. This reviewer recommends that this claim not be made in labeling as a study that shows lack of an adverse event in concert with lack of efficacy is not a representative examination of a drug's profile that has is actually efficacious in multiple other studies. More succinctly put, if there were lack of the event in the face of the positive effect, then it would be a more compelling argument for the claim.

The sponsor sites study 205 as a study supporting efficacy in the nonelderly adult population when it actually failed at the recommended dose on study nights 4-5 of a 5 day study.

The sponsor also states that zaleplon does not effect sleep stages and sites studies 203 and 204. Both of these studies failed to be more effective than placebo at crucial time points at the recommended dose (10 mg). It is not a compelling argument to suggest that lack of this adverse event in these relatively small studies suggests that the event actually does not occur when the primary effect off the drug is likewise not measurably present. Again, lack of the event in the face of presence of the primary effect would be a more compelling argument.

The remainder of the phase II placebo controlled sleep lab studies (201, 202, and 207 in addition to 203, 204 and 205 mentioned above) are reviewed for efficacy with respect to latency to persistent sleep (LPS).

Study 201-US A 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

Investigators and locations
This was a three center study. Investigators and sites were as follows:

June Fry, MD, Ph.D. n=15 Sleep Disorders Center The MCP at EPPI 3200 Henry Avenue Philadelphia, PA 19129	German Nino- Murcia, MD n=25 Sleep Medicine and Neuroscience Institute San Antonio Road Palo Alto, CA 94303	Gerald W. Vogel, MD n=10 Sleep Research Lab., Inc. 8 Executive Park West Suite 815 Atlanta GA, 30329

Objectives
The main objectives of this study were to compare, by using polysomnographic (PSG) recordings and patient questionnaires, the effect of two doses (10 mg and 40 mg) of zaleplon; triazolam (Halcion, 0.25 mg) and placebo on the sleep performance of patients with a recent 6- month history of primary insomnia; to investigate the safety and tolerability of the two doses of zaleplon in patients with primary insomnia; and to evaluate possible residual effects of zaleplon in the morning after treatment by measuring performance on a psychometric test battery.

Study population
Patients were men and women aged 21-60 years with a diagnosis of primary insomnia.

Design
This was a phase II multicenter, double- blind, placebo- and active drug- controlled, four- way crossover, sleep laboratory study to evaluate the safety, tolerability, and efficacy of two doses of zaleplon administered to patients with primary insomnia.

Assessments
A schedule of assessments performed in the study may be found in table 201.1.

Analysis Plan
The primary efficacy variable was latency to persistent sleep

(LPS).

Patient Disposition
Fifty patients comprise the ITT treatment population of the study. Three patients discontinued treatment before the end of the double- blind phase of the study. Patient 20109- 1024 was withdrawn after treatment 1 (zaleplon 40 mg) because of a positive urine drug screen (phenobarbital) during screening and treatment 1. Patient 20109- 1026 was withdrawn after treatment 3 (triazolam intended; placebo actual) due to a dosage error. Patient 20109- 1040 was discontinued after treatment 3 (triazolam) because of a positive urine drug screen (patient took Fiorinal, which contains 50 mg of butalbital, 40 mg caffeine, and 325 mg of aspirin).

Results

Table 201.2 Latency to persistent sleep study 201-US

Sleep Parameter	Screening	Placebo	Zaleplon 10 mg	Zaleplon 40 mg	Triazolam 0.25 mg	Significant Differences a
Latency to persistent sleep (min)	54.2 (3.8)	37.5 (3.5)	22.5 (2.3)	18.6 (2.6)	27.5 (2.1)	Z40< Z10
						Z40< TRZ
						Z40< placebo
						Z10< placebo
						TRZ< placebo

a: Statistically significant differences were determined based on the least squares means from the ANOVA model. Differences with p- values less than 0.05 are considered statistically significant. Z40 = zaleplon 40 mg, Z10 = zaleplon 10 mg, and TRZ = triazolam.

Conclusions
This study represents a positive study supporting zaleplon 10 mg as a more effective treatment than placebo at decreasing LPS.

Study 202-US A PHASE II MULTICENTER, DOUBLE- BLIND, PLACEBO-CONTROLLED, RANDOMIZED, FOUR- WAY CROSSOVER, SAFETY, TOLERABILITY, AND POLYSOMNOGRAPHIC STUDY COMPARING 20- mg AND 60- mg DOSES OF ZALEPLON, 0.25 mg OF TRIAZOLAM, AND PLACEBO IN PATIENTS WITH PRIMARY INSOMNIA

Investigators and locations
This was a two site study as follows:

Leon D. Rosenthal, MD Thomas Roth, PhD Henry Ford Hospital 2921 West Grand Boulevard Detroit, MI 48202	Gerald W. Vogel, MD Sleep Research Laboratory, Inc. 8 Executive Park West Suite 815 Atlanta, GA 30329

Objectives
The main objectives of this study were to compare, by using polysomnographic (PSG) recordings and patient questionnaires, the effect of two doses (20 mg and 60 mg) of zaleplon, triazolam, 0.25 mg, and placebo on the sleep performance in patients with a recent 6-month history of primary insomnia; to investigate the safety and tolerability of the two doses and to evaluate possible residual effects of zaleplon in the morning after treatment by using a battery of psychometric tests.

Study population
Men and women without child- bearing potential who were 21 to 60 years of age and had a diagnosis of primary insomnia. The diagnosis was based on the patient's reports of symptoms of insomnia with at least a 6- month recent history of sleep disturbances occurring at least three times a week on average. The patient also had to meet 2 of the following criteria: typical or modal sleep latency of at least 30 minutes, frequent nocturnal awakenings (three or more per night) with difficulty returning to sleep, and/ or total sleep time (TST) between 180 and 360 minutes, inclusive, with concomitant complaints of daytime tiredness or fatigue (averaging at least three times per week). Forty-three patients enrolled and 36 patients completed the study.

Design
This was a phase II multicenter, double- blind, placebo- and active drug- controlled, four- way crossover, sleep laboratory study to evaluate the safety, tolerability and efficacy of two doses of zaleplon administered to patients with primary insomnia.

Assessments
The schedule of assessments may be found in table 202.1 in the appendix.

Analysis Plan
Primary efficacy variables were the latency to persistent sleep (LPS) and total sleep time (TST) from the PSG recordings that were performed for a fixed time of 480 minutes (total time in

bed).

Patient Disposition

Forty-three patients comprised the ITT treatment population. Seven patients dropped out of the study (26 men; 17 women). Table 202.2 summarizes reasons for dropout.

Table 202.2 Reasons for dropout in study 202-US

Treatment Sequence	Patient Number	Age	Sex	Reason for Not Completing the Study
1 a	20208-1140	34	Male	Positive urine drug screen: cocaine in urine during treatment 1.
2 b	20208-1101	34	Male	After night 1 of treatment 1, patient's veins were considered too fragile for the number of blood draws required.
2	20208-1110	44	Female	After night 1 of treatment 2, patient experienced hallucinations and withdrew form the study.
2	20208-2101	34	Female	After night 1 of treatment 1, patient was offered a job and withdrew from the study.
2	20208-2110	22	Male	After treatment 2, patient withdrew from the study for personal reasons.
3 c	20208-1115	21	Male	After night 1 of treatment 4, patient withdrew from the study for personal reasons.
3	20209-1131	36	Male	Positive urine drug screen: THC in urine after treatment 2.

a: Zaleplon (60 mg), zaleplon (20 mg), triazolam (0.25 mg), placebo
b: Triazolam (0.25 mg), zaleplon (60 mg), placebo, zaleplon (20 mg)
c: Placebo, triazolam (0.25 mg), zaleplon (20 mg), zaleplon (60 mg)

Results

Results of LPS follow in table 202.3

Table 202.3 Results of LPS by treatment in study 202-US.						
Sleep Parameter			Zaleplon	Zaleplon	Triazolam	Significant
	Screening	Placebo	20 mg	60 mg	0.25 mg	Differences a
LPS (min)	58.3 (4.0)	47.0 (5.1)	30.5 (5.3)	21.7 (4.9)	27.6 (3.6)	Z60< Z20
						Z60< TRZ
						Z60< placebo
						Z20< placebo
						TRZ< placebo

a: Statistically significant differences were determined from the least squares means from the ANOVA model.
Differences with p- values less than 0.05 are considered statistically significant.
Z20 = zaleplon 20 mg, Z60 = zaleplon 60 mg, and TRZ = triazolam.

Conclusions
This study represents a positive study with regard to LPS for zaleplon 20 mg. All doses in this study were higher than the sponsor's suggested recommended dose of 10 mg. This short term study does not add any information to the phase three studies regarding effectiveness of the 20 mg over the 10 mg dose in longer term use.

Study 203-US A 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

Investigators and locations
The investigators (their investigator identification numbers) and site addresses are listed in the appendix in table 203.1. This is a 10 center study.

Objectives
The objectives of the study were to determine the safety, tolerability, and efficacy, evaluated by polysomnographic (PSG) recording and subjective evaluations of zaleplon (5 mg and 10 mg) in comparison with triazolam (0.25 mg) and placebo in patients with primary insomnia.

Study population
The study population consisted if 132 men and women patients with primary insomnia. Patients were aged 18-60 and women of child-bearing potential were neither pregnant nor breast feeding. Patients also had to meet PSG sleep impairment requirements as follows:

1. LPS on at least one of nights -2 and -1 was at least 20 minutes with neither of the nights having latency less than 15 minutes. Additionally, latency did not exceed 90 minutes on nights -2 and -1.

2. In the 480- minute recording period each screening night, TST was greater than 240 minutes on nights -2 and -1. TST did not exceed 420 minutes on more than one of the nights and did not exceed 430 minutes on either night.

3. On night -3 had an average of no more than 5 episodes of apnea plus hypopnea per hour

4. On night -3 had a maximum of 10 PLMs per hour. Of the 10 total PLMs, there were no more than 5 PLMs per hour that resulted in arousal.

Patients who did not meet the PSG entrance criteria could not be rescreened at a later time for entry into this study.

Design
This was a phase II, 10 center, double-blind, comparative, placebo-controlled, randomized, parallel group study in patients with primary insomnia. Eligible patients were randomly assigned to one of four treatment groups and received zaleplon 5 mg, zaleplon 10 mg, triazolam, or placebo for 14 nights during the double-blind phase of the study. The treatment arms were balanced, and patients were randomly assigned to a treatment within each trial center.

Assessments
A schedule of assessments is listed in table 203.2 in the appendix.

Analysis Plan
The primary efficacy variable was the LPS.

Values for time points for multiple nights were calculated by taking the mean of all nights in the interval. Specifically, the baseline time point was the average of the last two nights before double- blind treatment (nights -2 and -1); values for nights 1 and 2 were averaged and the average is called summary night 1- 2. Values for nights 13 and 14 were averaged and the average is called summary night 13- 14 . Values for nights 12 to 14 were averaged and the average is called summary night 12- 14.

The home period was the average of nights 3 through 11 and is called summary night 3- 11. Only questionnaire data were collected during the home period.

Patient Disposition
Six hundred seventy- three (673) patients were screened for the study; 541 were ineligible (234 of these because they failed the PSG screen). One hundred thirty- two (132) patients were randomly assigned to one of 4 treatment groups.

All 132 randomized patients had completed the placebo run- in period and received randomly assigned study medication under double- blind conditions. All 132 patients were included in all safety analyses. All of these 132 patients also met the ITT criteria and therefore are included in the ITT analysis.

A total of 7 (12.0%) patients discontinued treatment, 4 before the end of the double- blind phase of the study and 3 during the placebo run- out period.

Results
Results of the ITT observed case analysis of study 203-US may be found in the appendix. LPS was significantly shorter than placebo on the night 1-2 measurement but not significantly different than placebo throughout the remainder of the study. This was also true of the active comparitor triazolam.

Conclusions
This represents a failed study except for nights 1-2 where LPS was significantly shorter for zaleplon 5 and 10 mg than placebo. The 5 mg dose actually had a greater effect on night 1-2 than the 10 mg dose.

Study 204 EU A PHASE II, 28- DAY, MULTICENTER, 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

Investigators and locations
The investigators, their investigator identification numbers, numbers of patients at each site, and site addresses are listed in the appendix in table 204.1.

Objectives
The objectives of study 204-EU were a) To compare, with

polysomnographic (PSG) recordings and patient sleep questionnaires, the long- term (28- day) efficacy of 10 mg and 20 mg of zaleplon with those of 10 mg of zolpidem and placebo on the sleep performance of patients with a history of primary insomnia of at least 1 month's duration; b) to investigate the long- term (28- day) safety and tolerability of 10 mg and 20 mg of zaleplon in patients with primary insomnia; c) to investigate, after 28 days of treatment, discontinuation phenomena, including rebound insomnia, daytime anxiety, pharmacologic tolerance, psychomotor effects, and memory deficits associated with zaleplon.

Study population
Patients who were at least 18 years old and no more than 60 years old and who had primary insomnia. The diagnosis was based on documented subjective reporting of a history of sleep disturbance occurring at least three times per week for at least the previous month, as defined by Diagnostic and Statistical Manual, 3rd edition, revised (DSM- IIIR). Criteria for the PSG recordings, the latency to persistent sleep (LPS) had to be > 20 minutes on at least one of nights -2 and -1, with neither night having an LPS less than 15 minutes. LPS could not exceed 90 minutes on either night.

Design
This was a phase II, multi- center, randomized, double- blind, zolpidem- and placebo- controlled, parallel group study to investigate the 28 days safety and tolerability of zaleplon given at doses of 10 and 20 mg and its effectiveness as a hypnotic in patients with primary insomnia. Patients were randomly assigned to one of the four treatment groups and the treatment arms were balanced within each trial center.

Assessments
A schedule of assessments is listed in table 204.2 in the appendix.

Analysis Plan
PSG parameters for Summary Nights 1- 2, 13- 14, and 27- 28 were calculated by averaging the values of the individual nights. The primary efficacy analysis was performed on the observed cases Intent- to- Treat (ITT) data set by using LPS on Summary Night 27- 28 as the primary endpoint.

Patient Disposition
131 patients enrolled and were analyzed for safety, 122 completed the study. 130 were analyzed in the intent -to- treat (ITT)

population. Nine of the 131 patients discontinued prior to the end of the double blind treatment phase. One patient did not meet criteria to be included in the ITT population. One patient dropped out due to an adverse event in the placebo group.

There were no statistically significant differences in age, sex, ethnic origin, or severity of symptoms.

Results

LPS was significantly shorter in the zaleplon 10 mg and zaleplon 20 mg treatment groups than in the placebo group on Summary Night 1- 2 (zaleplon 10 mg vs placebo, Dunnett's test p= 0.026, zaleplon 20 mg vs placebo, Dunnett's test p< 0.001). On Summary Night 13- 14 and the primary study end point, Summary Night 27-28, there was no significant difference between zaleplon and placebo. However, in the zaleplon 10 mg treatment group, the median LPS tended to be shorter than in the placebo group.

The ANCOVA analysis indicated there was no significant difference between zolpidem 10 mg and placebo on any of the Summary Nights. However, there was a trend toward a shorter LPS in the zolpidem 10 mg treatment group than in the placebo group (p= 0.053) on Summary Night 1- 2.

Conclusions

This study represents a failed study for the primary efficacy variable. Zaleplon was only better than placebo on nights 1-2.

In labeling the sponsor references study 204-EU while making the argument that zaleplon does not lead to increased numbers of awakenings in the last quarter of sleep. There is no analysis to support this statement. In fact the number of awakenings after onset of persistent sleep (NAASO) was significantly greater than placebo in the zaleplon 20 mg group at night 13-14 and 27-28, and in the zaleplon 10 mg at night 13-14. These analyses are not broken down by period. A more useful analysis might be the NAASO in the last half of the night.

Study 205 EU/CA

Investigators and locations

A list of investigators and study sites is listed in table 205.1 in the appendix.

Objectives

The main objective of this study was to investigate the short-term (5- day) efficacy, safety, and tolerability of zaleplon 2, 5, 10, and 20 mg as a hypnotic in patients with primary insomnia.

Study population
Men and non- pregnant women 18 to 60 years of age with a diagnosis of primary insomnia based on documented patient reporting of a history of sleep disturbance occurring at least three times per week for at least the previous 1 month, as defined by DSM- IIIR.

Design
This was a phase II, multicenter, randomized, double- blind, placebo- controlled, parallel- group study conducted to investigate the short- term (5- day) safety and tolerability of four doses of zaleplon and its effectiveness as a hypnotic in patients with primary insomnia. The treatment arms were balanced and patients were randomly assigned consecutively at each study center. A minimum of 100 patients were planned, with a minimum of 10 and a maximum of 20 per group.

Assessments
A schedule of assessments performed in the study may be found in table 205.2.

Analysis Plan
The primary efficacy variable was LPS as measured by PSG data. Each PSG recording was scored manually in 30- second epochs. Information about the patient's perception of the effects of time to sleep onset (TSO) were collected from sleep questionnaires.

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
The 137 patients who completed the single- blind placebo period, received randomly assigned study medication under double- blind

conditions, and for whom on- therapy data were collected are included in all safety analyses. None of these patients were excluded from the intent- to- treat analysis.

Table 205.3 Patient disposition Study 205			
	N total	Zaleplon	Placebo
Total Safety population	137	109	28
Total withdrawals	4	3	1
Adverse dropouts	1	1	0

Results
Results of the ITT analysis of the observed cases with respect to LPS show that zaleplon 10 and 20 mg was effective on night 1-2 but only the 20-mg dose was effective on night 4-5.

Conclusions
Zaleplon 10 and 20 mg were superior to placebo on night 1-2 but only 20 mg was superior on night 4-5. This study is equivocal in that 10 mg (the suggested dose) was only superior to placebo at the first time point. The placebo response was quite large and may mitigate in favor of the study being a failed study as opposed to a negative study at the 10 mg dose.

Study 207 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

Investigators and locations
The investigators (their investigator identification numbers) and site addresses are as follows:

David Berkowitz, MD (20729)
n = 12
Center for Sleep Disorders
1275 E. Kemper Road
Cincinnati, OH 45246

Charles W. Erwin, MD (20730)
n = 13
Sleep Disorders Lab

Kenneth Moss, MD (20732)
n = 12
Sleep Disorders and Research Center
Deaconess Hospital
St. Louis, MO 63139

Gary Richardson, MD (20733)
n = 4
Brigham & Women's Hospital

Duke University	221 Longwood Ave., Rm 460
Durham, NC 27710	Boston, MA 02115
June Fry, MD (20731)	Gerald W. Vogel, MD (20734)
n = 4	n = 9
Sleep Disorders Center	Sleep Research Laboratory
Medical College of Pennsylvania at EPPI	Executive Park West
Philadelphia, PA 19129	Atlanta, GA 30329

Objectives
To compare, with polysomnographic (PSG) recordings and patient questionnaires, the effects of 2, 5, and 10 mg of zaleplon with those of placebo in elderly patients with a history of chronic insomnia (ie, difficulty initiating and/ or maintaining sleep) for at least 3 months before initial screening.

Study population
Fifty-four noninstitutionalized men and women 60 through 80 years of age with a diagnosis of insomnia based on patients' reports of a history of sleep disturbances averaging at least three times per week for at least the prior 3 months, without any major psychiatric disorders or clinically important medical illnesses and with sleep-associated daytime complaints.

Design
This was a phase II, multicenter, randomized, double- blind, placebo- controlled, four- way crossover, sleep laboratory study to investigate the safety, tolerability, and hypnotic efficacy of three doses of zaleplon in elderly patients with primary insomnia. Patients were randomly assigned to one of four treatment sequences according to a balanced Latin- square design. A minimum of 48 patients were planned. Each center planned to enroll a minimum of 8 and a maximum of 16 patients.

Assessments
A schedule of the assessments is listed in the appendix in table 207.1.

Analysis Plan
The primary efficacy variable was LPS. Efficacy analyses were performed on the observed case patient group. Efficacy variables were analyzed by using methods of analysis of variance (ANOVA) with the following factors: sequence, investigator, sequence by investigator, treatment, period, and patient nested within

sequence by investigator. Dunnett's test was used for multiple comparisons of zaleplon- treated groups with placebo. Pairwise comparisons were made regardless of whether the overall difference between treatment groups was statistically significant.

Patient Disposition

Three hundred eleven (311) patients entered the initial screening phase. Of those patients, 219 met the general screening criteria and entered the PSG screening phase (placebo run- in period). The 54 patients who met the PSG screening criteria and received randomly assigned study medication under double- blind conditions were included in all safety analyses.

Results

Results of TSO and LPS follow in table 207.2 .

Table 207.2 Results and analysis of LPS and TSO in study 207-US (observed cases)

Sleep Parameter	Treatment Group	Number Patients		p- Value Different from			Dunnett
			Median	2 mg	5 mg	10 mg	Control (Placebo)
LPS (minutes)	Placebo	48	30.1	.015	<.001	<.001	
	2 mg Zal	48	27.0		.018	<.001	.038
	5 mg Zal	48	23.4			.012	<. 001
	10 mg Zal	48	14.6				<. 001
TSO (minutes)	Placebo	48	45.0	.654	.017	<.001	
	2 mg Zal	48	43.8		.052	<.001	.944
	5 mg Zal	48	30.0			.014	.043
	10 mg Zal	48	25.0				<. 001

Conclusions

This study supports the hypothesis that zaleplon 5 and 10 mg is more effective than placebo at decreasing LPS. TSO, a secondary variable in this protocol was also significantly shorter than placebo.

/S/ [redacted]

APPEARS THIS WAY ON ORIGINAL

7/27/98

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]

/S/ [redacted]

TL, DDS

Table 201.1 Scedule of assessments for study 201-US							
	Baseline Eligibility Phase	PSG Screening Phase			Treatment Phase a		Posttreatment Phase
Procedure		Night			Night		
		1	2	3	1	2	Final Visit
Sleep history	X						
Inclusion criteria	X						
Exclusion criteria	X						
PSG inclusion criteria				X b			
Urine drug screen	X	X	X	X	X	X	
Breath alcohol test		X	X	X	X	X	
Medical history	X						
Physical exam	X	X			X	X	X
Vital signs	X	X	X	X	X	X	X
Neurologic exam	X	X		X	X	X	X c
Hematology	X	X			X	X	X c
Blood chemistry	X	X			X	X	X c
Urinalysis	X	X			X	X	X c
Chest radiograph d	X						
12- Lead ECG e	X						X c
Thermistors		X					
Monitoring of PLMs		X	X				
Clinical EEG	X						
Presleep questionnaire		X	X	X	X	X	
Study drug		X	X	X	X	X	
administration							
PSG EEG		X	X	X	X	X	
Postsleep questionnaire		X	X	X	X	X	
Psychometric tests		X	X	X	X	X	
Study events		X	X	X	X	X	X

a: Includes four treatment periods of 2 consecutive days each, followed by a 5- or 12- day washout period.

b: If patient met PSG inclusion criteria, he/ she was randomized into the treatment phase.

c: These evaluations were required only if there was an abnormal result at the last treatment period.

d: If a chest radiograph with normal results had been performed within 12 months before screening, a written report of those results could be substituted.

e: Cardiac monitoring during the PSG screening phase and all treatment phases was through analysis of the V5 cardiac lead during the 8- hour period.

Table 202.1 Scedule os assessments for study 202-US							
Procedure	Baseline Eligibility	PSG Screening Phase Night			Treatment Phase a Night		Posttreatment Phase
		1	2	3	1	2	Final Visit
Sleep history	X						
Inclusion criteria	X						
Exclusion criteria	X						
PSG inclusion criteria				X b			
Urine drug screen	X	X	X	X	X	X	
Breath alcohol test		X	X	X	X	X	
Medical history	X						
Physical exam	X	X			X	X	X
Vital signs	X	X	X	X	X	X	X
Neurologic exam	X	X		X	X	X	X c
Hematology	X	X			X	X	X c
Blood chemistry	X	X			X	X	X c
Urinalysis	X	X			X	X	X c
Chest radiograph d	X						
12- lead ECG e	X						X c
Thermistors		X					
Monitoring of PLMs		X	X				
Clinical EEG	X						
Presleep questionnaire		X	X	X	X	X	
Study drug administration		X	X	X	X	X	
PSG EEG		X	X	X	X	X	
Postsleep questionnaire		X	X	X	X	X	
Psychometric tests		X	X	X	X	X	
Study events		X	X	X	X	X	X

a: Includes four treatment periods of 2 consecutive days each, followed by a 5- or 12- day washout period.

b: If patient met PSG inclusion criteria, he/ she was randomized into the treatment phase.

c: These evaluations were required only if there was an abnormal result at the last treatment period.

d: If a chest radiograph with normal results had been performed within 12 months before screening, a written report of those results could be substituted.

e: Cardiac monitoring during the PSG screening phase and all treatment phases was through analysis of the V5 cardiac lead during the 8 hour period.

Table 203.1 Investigators and sites for study 203-US	
Sigurd H. Ackerman, MD (20338) n = 6	David Neubauer, MD (20339) n = 4
Sleep Disorders Institute	Johns Hopkins Sleep Disorders Center
St Luke's/ Roosevelt Hospital	Francis Scott Key Medical Center
New York City, NY, US 10025	Baltimore, MD, US 21224
David Berkowitz, MD (20334) n = 16	Leon D. Rosenthal, MD (20341) n = 7
Center for Sleep Disorders	Sleep Disorders Center
E. Kemper Road	Henry Ford Hospital
Cincinnati, OH, US 45246	Detroit, MI, US 48202
Milton K. Erman, MD (20340) n = 6	Gerald W. Vogel, MD (20335) n = 16
Sleep Disorders Center	Sleep Research Laboratory
Scripps Clinic & Research Foundation	Executive Park West
LaJolla, CA, US 92037	Atlanta, GA, US 30329
Charles W. Erwin, MD (20332) n = 19	Kenneth Moss, MD (20333) n = 16
Sleep Disorders Lab	Sleep Disorders & Research Center
Duke University	Deaconess Hospital
Durham, NC, US 27710	St. Louis, MO, US 63139
June Fry, MD (20337) n = 18	Ismet Karacan, MD (20336) n = 24
Sleep Disorders Center	Sleep Disorders Center
Medical College of Pennsylvania at EPPI	Baylor College of Medicine
Philadelphia, PA, US 19129	Texas Medical Center
	Houston, TX, US 77030

Table 203.2 Schedule of assessments for study 203-US

		Placebo (night)		Double- Blind Treatment (night)				Placebo
	Initial	-3	-2 to -1	1 to 2	3 to 11	12	13 to 14	+1 to +2
Procedure	Screening		(Run- in)		(Home)	(Readaptation)		(Run- out)
PSG recording a		X b	X b	X		X	X	X
Study drug administration		X	X	X	X	X	X	X
Medical and sleep history	X							
Inclusion criteria	X							
Exclusion criteria	X							
PSG inclusion criteria		X						
Drug screen/ breath alcohol test	X	X c				X c		
Physical examination d	X	X e						X e
Neurological examination	X	X e						X e
Laboratory tests f	X	X e, g		X e, h			X e	X e
ECG d	X							X e
Adverse experiences i		X	X	X	X	X	X	X
Vital signs d, e	X	X	X	X		X	X	X
Impairment evaluation e		X	X	X			X	X
Zung anxiety/ depression	X							
Tyrer symptom checklist			X				X	X
Self- evaluation questionnaires j		X	X	X			X	X

a: PSG = polysomnographic.

b: Night -3 was for adaption and qualification. PSG screening data from nights -2 and -1 were used for qualifying and as baseline data from data for later time point Nine nights were scored at a central location

c: Assessed before study drug administration in the sleep laboratory. The drug screen included amphetamines, cocaine, opiates, benzodiazepines, cannabis, barbiturates, and alcohol.

d: Procedures were done at the final visit for patients who withdrew from the study.

e: Assessed or completed in the morning following the sleep period.

f: If applicable, pregnancy tests (HCG) were done at initial screening, night -3, and on run- out night +2, or at the final visit for patients who discontinued early.

g: Patients with laboratory test results in the placebo PSG screening phase (night -3) that violated the inclusion/ exclusion criteria were removed from the study.

h: Repeated on night 2 only if the previous examination test result was abnormal. Could be repeated as needed.

i: Patients who had an adverse reaction rated as moderate or worse in severity during the placebo PSG screening phase (nights -3 to -1) were excluded from the stu

j: Done/ started in the evening.

k: Memory tests were digit span and visual memory test.

l: Psychomotor tests were simple reaction time, complex reaction time, and digit symbol substitution.

Table 204.1 Investigators and sites in study 204-EU	
H. Allain, MD (20422) Laboratoire de Pharmacologie Clinique Faculté de médecine Avenue L. Bernard 35043 Rennes France n= 4	L. Arbus, MD (20420) C. H. U Rangueil Avenue du Pr. Poulhès 31054 Toulouse Cedex France n= 8
M. Billiard, MD (20430) Hôpital Gui de Chauliac Avenue Bertin Sans 34295 Montpellier Cedex 05 France n= 8	F. Canellas, MD (20423) Unidad de psiquiatria Hospital San Dureta c/ Andrea Doria n° 55 Palma de Mallorca 07014 Spain n= 10
R. Cluydts, MD (20428) Universitair Ziekenhuis Wilrijkstraat 10 B- 2520 Edegem Belgium n= 16	J. Espinar, MD (20427) Hospital universitario San Carlos 28040 Madrid Spain n= 1
E. Estivill, MD (20418) Instituto Dexeus Unidad de alteraciones del sueno Paseo de la Bonanova, 61 bajos Barcelona Spain n= 20	H. A. C. Kamphuisen, MD (20417) Academic hospital, University of Leiden PO Box 9600 2300 RC Leiden-08017- The Netherlands n= 12
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M. Schittecatte, MD (20425) Hôpital Vincent Van Gogh Chef de service f. f. B- 6030 Marchienne- au- Pont Belgium n= 12	

Table 204.2 Schedule of assessments for study 204-EU

	INITIAL SCREENING	POLYSOMNOGRAPHIC SCREENING			RANDOMISED TREATMENT PHASE											PLACEBO RUN- OUT	
	NIGHTS	-3	-2	-1	1	2	3	4... 12	13	14	15.. 25	26	27	28		+1	+2
MEDICAL + SLEEP HISTORY	X																
INCLUSION/ EXCLUSION	X																
POLYSOMNOGRAPHIC RECORDING		X	X	X	X	X		X	X	X		X	X	X		X	X
DRUG SCREEN	X	X						X				X					X
BREATHALYSER	X	X	X	X	X	X		X	X	X		X	X	X		X	X
PHYSICAL EXAMINATION	X	X															X
VITAL SIGNS	X	X	X	X	X	X		X	X	X		X	X	X		X	X
IMPAIRMENT ASSESSMENT	X	X	X	X	X	X		X	X	X		X	X	X		X	X
LABORATORY TESTS	X	X			X									X			X
PREGNANCY TEST	X	X															X
URINE HCG																	
ROUTINE ECG	X																X
DRUG ADMINISTRATION			X	X	X	X	X	X	X	X	X	X	X	X		X	X
ADVERSE EXPERIENCES		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
HABITAT *		L	L	L	L	L	H	H	L	L	H	L	L	L		L	L

*L= Sleep lab; H=Home

Table 204.3 Observed Case Analysis (204-EU) X=median latency to persistent sleep (LPS) ITT patients								
Treatment Groups	Treatment nights							
	Baseline		1-2		13-14		27-28	
	n	X	n	X	n	X	n	X
Zaleplon 10 mg	34	40.4	34	22.9	34	23.0	34	22.3
Zaleplon 20 mg	31	47.8	31	17.3	31	23.8	31	25.0
Zolpidem 10 mg	33	48.0	33	25.8	33	26.8	33	30.7
PLACEBO	32	48.0	32	30.0	32	31.3	32	24.6
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem								
Zaleplon 10 mg vs Placebo			.03		.16		.57	
Zaleplon 20 mg vs Placebo			<.001		.24		.89	
Zolpidem 10 mg vs Placebo			.05		.20		.47	

Table 205.1 List of investigators for study 205 EU/CA	
Prof. P. Clarenbach (20513) n = 10 Neurologisches Johanneskrankenhaus Schildescherstr. 99 33611 Bielefeld, Germany	Dr. H. Moldofsky (20518) n = 15 Dept. of Psychiatry The Toronto Hospital, Western Division 399 Bathurst Street, Room ECW3D- 022 Toronto, Ontario M5T 2S8, Canada.
Dr. B. Dietrich (20515) n = 25 LAB GmbH & Co. Wegenerstr. 13 89231 Neu- Ulm, Germany	Prof. J. de Roeck (20521) n = 15 Centrum Voor Klinisch Slaaponderzoek Dienst Psychiatrie Universitair Ziekenhuis Antwerpen Wilrykstraat 10 2650 Edegem, Belgium.
Asst. Prof. J. Hetta (20512) n = 20 Sleep Disorders Unit University Hospital 751 85 Uppsala, Sweden	Prof. E. Rüther (20514) n = 10 Psychiatrische Universit@ tsklinik Göttingen Von Siebold Str. 5 37075 Göttingen, Germany
Dr. F. Hohagen (20520) n = 5 Psychiatrische Universitätsklinik Hauptstr. 5 79104 Freiburg, Germany.	
Prof. H. Kamphuisen (20522) n = 15 Westeinde Ziekenhuis Slaapcentrum KNF Lijnbaan 32 2512 VA Den Haag the Netherlands.	Dr. H. Schulz (20516) n = 20 Parexel GmbH Universitätsklinikum Rudolf Virchow Haus 18 Spandauer Damm 130 14050 Berlin, Germany
Dr. M. Kryger (20523) n = 2 St. Boniface General Hospital Research Center - Sleep Laboratory 351 Tache Ave. Winnipeg, Manitoba R2H 2A6, Canada.	

Table 205.2 Schedule of assessments study 205 EU/CA

	Initial		Polysomnographic Screening				Double- Blind Treatment Phase			(Placebo Run-out)	
Procedure /Nights	Screening a	-3	-2	-1	1	2	3	4	5	+1	+2
Medical & sleep history b	X										
Inclusion/ exclusion c	X										
Drug screen	X	X							X d		Xd
Breath alcohol	X	X	X d	X d	X d	X d	X d	Xd	X d	X d	Xd
Physical examination e	X	X f									Xf
Vital signs e	X	X f	X f	X f	X f	X f	X f	X f	X f	X f	Xf
Impairment assessment e	X	X f	X f	X f	X f	X f	X f	X f	X f	X f	Xf
Laboratory tests e	X	Xf, g			X f	X f, h			X f		Xf
Pregnancy tests (if applicable)											
Serum HCG	X										Xf
Urine HCG		X									
12- lead ECG e	X										Xi
Polysomnographic recording		X j	X j	X j	X	X	X	X	X	X	X
Sleep questionnaires k		X	X	X	X	X	X	X	X	X	X
Tyrer symptom checklist l				X	X				X	X	X
Placebo administration			X	X						X	X
Study drug administration					X	X	X	X	X		
Study events l		X	X	X	X	X	X	X	X	X	X

a: Performed after a 7- to 14 day washout during which pre- and postsleep questionnaires were completed for 7 days, and up to 14 days before the start of PSG screening.

b: Included pre- and postsleep questionnaires, completed by the patient during the 7 washout days.

c: Including Zung A and Zung D self- rating scales.

d: Before dose administration in the sleep laboratory.

e: Procedures had to be done at final visit for early dropouts.

f: Assessed/ completed in the morning after sleep recording.

g: Patients with laboratory test results on night -3 that violated the inclusion/ exclusion criteria were withdrawn from the study.

h:. Only if abnormal in previous test result. Retest done as needed.

i: Assessed/ completed in the evening, before dose administration, or in the morning after other assessments

j: Night -3 was for adaptation. PSG screening data from nights -2 and -1 were to be used for screening and as baseline data.

k: Presleep questionnaire was completed before dose administration in the sleep laboratory, and postsleep questionnaire was completed in the morning, after sleep recording.

l: Any patient experiencing a study event rated as moderate or severe during the PSG screening phase (nights -3 to -1) was excluded from the study.

Table 205.4 OBSERVED CASE ANALYSIS (205-EU/CA)
X=Median latency to persistent sleep, ITT patients

Treatment Groups	Treatment time point					
	Baseline		Night 1-2		Night 4-5	
	n	X	n	X	n	X
Zaleplon 2 mg	28	35.3	28	27.0	27	23.5
Zaleplon 5 mg	27	41.3	27	27.2	27	22.8
Zaleplon 10 mg	27	46.5	27	19.8	25	14.8
Zaleplon 20 mg	27	49.5	27	14.5	27	14.8
PLACEBO	28	34.9	28	31.0	27	21.8
p-values for zaleplon Dunnett's test Control=placebo						
Zaleplon 2 mg vs Placebo			.82		1.0	
Zaleplon 5 mg vs Placebo			.20		.80	
Zaleplon 10 mg vs Placebo			.02		.17	
Zaleplon 20 mg mg vs Placebo			<.001		<.001	

Table 207.1 Schedule of assessments for study 207-US							
	Initial Screening	Polysomnographic Screening Phase			Treatment Phase a		Final Visit
		Night			Night		(Post treatment)
Procedure		-3	-2	-1	1	2	
Sleep history	X						
Medical history	X	X			X b		
Inclusion/ exclusion	X						
Physical exam	X	X			X c		X
Neurologic exam	X	X					
Laboratory tests	X	X				X d	X
Chest radiograph e	X						
12- lead ECG	X						X
Vital signs	X	X f	X f	X f	X f	X f	X
Urine drug screen	X	X g	X g	X g	X g	X g	
Breath alcohol test	X	X g	X g	X g	X g	X g	
Study drug administration		X	X	X	X	X	
PSG recording h		X	X	X	X	X	
Sleep questionnaires i		X	X	X	X	X	
Psychomotor tests j		X	X	X	X	X	
Study events		X	X	X	X	X	X

a: Including four treatment periods of 2 consecutive days each, followed by a 5- or 12- day washout period.

b: Before dose administration on night 1. If the results were not normal, treatment was postponed 1 week. Full physical or neurologic exams performed only if a study event had been reported.

c: Interim examination, performed in the morning after treatment on night 2 only if there had been a change in medical history.

d: Performed in the morning after treatment on night 2.

e: If a chest radiograph with normal results had been performed within 12 months before screening, a written report of those results could be substituted.

f: Done before and in the morning after dose administration.

g: Before each study drug treatment.

h: Beginning 30 minutes after drug treatment.

i: Presleep questionnaires completed before dose administration and sleep, and postsleep questionnaires completed the morning after recording in the sleep laboratory.

j: Including impairment evaluation. Completed the morning after recording in the sleep laboratory.

RECEIVED JUL 2 1 1998

Statistical Review and Evaluation

NDA#:20-859

JUL 2 1 1998

Applicant: Wyeth-Ayerst

Name of Drug: zaleplon

Documents Reviewed: Vols 1.356, 1.361, 1.364 1.369, 1.371, 1.379

Medical Officer: Paul Andreason, M.D., HFD-120

Background

The sponsor has submitted five (5), 3 in non-elderly and 2 in elderly patients), randomized, placebo controlled, parallel group, multicenter, double-blind trials in support of the efficacy and safety of zaleplon (zal) for the treatment of Insomnia. Trial **301** (non-elderly) was conducted in the US, **303** (non-elderly) in Europe and Canada, **306** (elderly) in the US, **307** (non-elderly) in the US and Canada, and **308** (elderly) in Europe. **This review examines the results of the primary endpoint, only: Time to Sleep Onset at Week 1.**

All tables and graphs are taken from the NDA submission

Trial 301

This was a 28-day trial with five groups: zal 5 mg (N=118), zal 10 mg (N=120), zal 20 mg (N=121), 10 mg Zolpidem (N=117), and placebo (N=119). There were 27 investigators. The **primary clinical endpoint was Time to Sleep Onset (TSO) during week 1 of therapy. Secondary endpoints included change in Total Time Slept (TTS), Number of Awakenings (NAW) and sleep quality at week 1.**

The study was designed to have 80% power to detect a difference of between 12 to 24 minutes in TSO between an active group and placebo, assuming a standard deviation between 30 and 60 minutes).

The **protocol states that change from baseline would be the unit of analysis where the value at** each week would be a "trimmed mean" of the number of observations taken during each week, the definition of the trimmed mean depending upon the number of observations taken for a particular patient. These changes from baseline were to be analyzed using ANOVA with factors for treatment group, center, and their interaction. For the primary clinical endpoint analysis (TSO), ANCOVA with baseline TSO as the covariate was to be used if TSO's were "not comparable at baseline" among the treatment groups. If the "overall" F-test was significant at the 5% level, then **Dunnett's** test would be used for multiple comparisons to placebo.

The reported results in the study report differ from the methods proposed in the protocol in 3 respects:

1) Simple means, rather than trimmed means are used.

2) The report analyzes the weekly mean with baseline mean as the covariate in ANCOVA, rather than the change from baseline mean.

3) The ranks of the observations are analyzed rather than the observed numbers due to what the sponsor call, violations of the assumptions necessary for ANCOVA.

4) Jonckheere's test was used to test for a dose response, both with and without placebo in the analysis.

Table 1 displays the demographic and baseline characteristics of the ITT population.

Table 2 displays the results for the TSO clinical endpoint for the **ITT observed cases population. Note that the Dunnett's test p-values are significant for zal 10 mg (.002) and zal 20 mg (<.001). Table 3** displays the group values using means. **Figure 1** displays the median TSO for each group over time, and **Figure 2** displays the empirical distribution functions (edf's) at week 1 (the primary time for the analysis).

Reviewer's Comments

The sponsor states that:

The statistical methodology of the original ACCO protocol was amended in order to achieve a global strategy for the analysis of the zaleplon clinical trials. This was done before the blind was broken.

However, it seems that the most appropriate analysis when analyzing the on-study mean would be survival analysis since TSO's are likely to be non-normally distributed. This reviewer has confirmed that the statistically significant results ($p < .001$) are maintained using **Cox regression on TSO at week 1 with baseline TSO as covariate**. In addition, a log transformation is adequate to "normalize" the TSO's whereupon statistical significance is maintained by either using **ANOVA with change in log TSO from baseline to week 1 as the unit of analysis** or **ANCOVA on the log TSO at week 1 with log baseline TSO as the covariate**. The difference in medians between zal 10 mg and placebo for TSO was about 17 **minutes** and that for zal 20 mg and placebo was about **22 minutes**.

Trial 307

This 14-day study was similar in design, clinical variables, and analysis as trial **301**. There were 39 investigators with a 2:2:1 weighted randomization among 3 treatment groups: either zal 10 mg for the full two weeks, zal 10 mg for the first week and zal 20 mg for the second week, or placebo for the full two weeks **Table 1** displays the demographic and baseline characteristics of the 3 treatment groups. **Thus *all* patients on active treatment at week 1 were on 10 mg**. See **Table 2** for a summary of results for TSO. **Table 3** indicates the significant difference between zal 10 mg and placebo at week 1. **Figure 1** displays means over time in each treatment group. The difference in medians between zal 10 mg and placebo was about **9 minutes**, about half of the difference which occurred between those two groups in trial **301**.

Figure 2 displays the edf's at week 1.

Reviewer's Comments

The three supplementary analyses used in confirming the sponsor's ranks analysis all confirmed p-values <.001 for the comparison between zal 10 mg and placebo.

Trial 303

This trial was identical in design to trial **301**. **Table 1** displays the demographic and baseline characteristics of the 5 treatment groups. **Table 2** displays the results for TSO indicating p-values of <.001 comparing either zal 10 mg or zal 20 mg to placebo. The difference between either zal 10 mg or zal 20 mg and placebo with respect to median TSO is approximately 15 minutes. **Figure 1** displays the mean TSO's over time and **Figure 2** displays the edf's at week 1.

Reviewer's Comments

The three supplementary analyses used in confirming the sponsor's ranks analyses all confirmed p-values in the range of .001 for the comparisons between zal 10 mg or zal 20 mg and placebo.

Trial 308

This trial enrolling **only patients at least 65 years old** was similar in design to those using non-elderly patients. **Table 1** displays the demographic and baseline characteristics of the 3 treatment groups. **Table 2** displays the results for TSO indicating p-values of <.001 comparing either zal 5 mg or zal 10 mg to placebo. The difference between the median TSO's between either dose and placebo is approximately 20 minutes. **Figure 1** displays median TSO's over time in each treatment group. There was no evidence that zal 10 mg was more effective than zal 5 mg. **Figure 2** displays the edf's at week 1.

Trial 306

This trial enrolling **only patients at least 65 years old** was similar in design to those using non-elderly patients. **Table 1** displays the demographic and baseline characteristics of the 3 treatment groups. **Table 2** displays the results for TSO indicating p-values of <.001 comparing either zal 5 mg or zal 10 mg to placebo. The difference between the median TSO's between either dose and placebo is approximately 20 minutes. **Figure 1** displays median TSO's over time in each treatment group. **There was no evidence that zal 10 mg was more effective than zal 5 mg. Figure 2** displays the edf's at week 1.

Conclusions

The sponsor has submitted 3 trials with non-elderly outpatients and 2 trials with elderly outpatients which statistically demonstrate the efficacy of zaleplon for insomnia. There is no substantial evidence that 10 mg is more efficacious than 5 mg in elderly subjects.

/S/

David Hoberman, Ph.D.
Mathematical Statistician

concur: Dr. Jin /S/

Dr. Chi /S/

cc:
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APPEARS THIS WAY ON ORIGINAL

STUDY 301

Table 1 (301)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR INTENT-TO-TREAT POPULATION

Characteristic	Descriptor	Placebo (n = 118)	Zaleplon 5 mg (n = 118)	Zaleplon 10 mg (n = 119)	Zaleplon 20 mg (n = 116)	Zolpidem 10 mg (n = 115)	p-Value
e (years)	Mean	43	43	40	41	42	0.223
	S.D.	12	12	10	13	11	
	Range	20-65	21-65	18-63	18-65	21-64	
Weight (kg)	Mean	79	77	77	74	77	0.307
	S.D.	17	16	15	16	19	
	Range	48-125	46-148	45-123	44-139	39-142	
Primary Diagnosis, N (%)	Primary insomnia	113 (96%)	113 (96%)	113 (95%)	111 (96%)	114 (99%)	0.486
	Psych. insomnia	5 (4%)	5 (4%)	6 (5%)	5 (4%)	1 (1%)	
Ethnicity, N (%)	Black	11 (9%)	17 (14%)	11 (9%)	15 (13%)	11 (10%)	0.453
	Hispanic	2 (2%)	4 (3%)	2 (2%)	4 (3%)	4 (3%)	
	Native American				1 (1%)		
	Oriental (Asian)	1 (1%)	2 (2%)	2 (2%)	1 (1%)	3 (3%)	
	Other	3 (3%)					
	White	101 (86%)	95 (81%)	104 (87%)	95 (82%)	97 (84%)	
Sex, N (%)	Female	64 (54%)	81 (69%)	64 (54%)	71 (61%)	62 (54%)	0.081
	Male	54 (46%)	37 (31%)	55 (46%)	45 (39%)	53 (46%)	
NAW	Mean	2.2	2.2	2.2	2.5	2.5	0.362
	S.D.	1	1.1	1.5	2.6	1.5	
	Range	1.0-6.1	1.0-8.5	1.0-15.3	1.0-27.3	1.0-8.9	
TSO - SQ (Minutes)	Mean	80	82	78	72	71	0.256
	S.D.	51	47	46	42	40	
	Range	24-320	18-240	20-258	19-234	24-275	
S - SQ (Minutes)	Mean	324	327	326	326	327	0.999
	S.D.	59	69	73	68	67	
	Range	171-461	57-481	76-512	107-460	103-476	

Table 2 (301)

TSO (MINUTES)-ITT PATIENTS: OBSERVED VALUE ANALYSIS
COMPARISONS BETWEEN GROUPS

Study Segment	Therapy Group	Number Patients	Median	p-Value Difference from 5 mg	p-Value Difference from 10 mg	p-Value Difference from 20 mg	p-Value Difference from Zolp 10 mg	p-Value Dunnett Control=Pbo (Ranks)	p-Value Jonckheere
PL Run-in	Placebo	118	66.43						
	5 mg Zaleplon	118	69.29						
	10 mg Zaleplon	119	62.50						
	20 mg Zaleplon	116	61.07						
	10 mg Zolpidem	115	60.71						
DB Week 1	Placebo	118	57.50	0.017	<.001	<.001	0.008		<.001 a
	5 mg Zaleplon	118	45.36		0.319	0.001	0.764	0.044	<.001 b
	10 mg Zaleplon	119	40.71			0.022	0.490	0.002	
	20 mg Zaleplon	116	35.71				0.003	<.001	
	10 mg Zolpidem	115	45.71						
DB Week 2	Placebo	113	49.29	0.465	0.043	<.001	0.502		<.001 a
	5 mg Zaleplon	113	43.57		0.197	0.001	0.959	0.806	<.001 b
	10 mg Zaleplon	113	36.43			0.037	0.183	0.108	
	20 mg Zaleplon	111	31.67				<.001	<.001	
	10 mg Zolpidem	109	46.43						
DB Week 3	Placebo	109	45.00	0.029	0.005	<.001	0.236		<.001 a
	5 mg Zaleplon	108	40.71		0.543	0.002	0.323	0.073	<.001 b
	10 mg Zaleplon	107	35.71			0.015	0.110	0.014	
	20 mg Zaleplon	104	30.00				<.001	<.001	
	10 mg Zolpidem	105	44.29						
DB Week 4	Placebo	107	47.14	0.569	0.032	<.001	0.033		<.001 a
	5 mg Zaleplon	101	45.63		0.123	<.001	0.124	0.895	<.001 b
	10 mg Zaleplon	102	35.00			0.034	0.988	0.082	
	20 mg Zaleplon	101	30.00				0.037	<.001	
	10 mg Zolpidem	98	34.29						
PL Run-out	Placebo	106	45.00	0.987	0.936	0.404	0.009		0.139 a
	5 mg Zaleplon	98	45.00		0.925	0.407	0.012	0.999	0.076 b
	10 mg Zaleplon	100	43.33			0.458	0.008	0.999	
	20 mg Zaleplon	98	34.17				<.001	0.739	
	10 mg Zolpidem	96	65.00						

a: Jonckheere Test Including Placebo

b: Jonckheere Test Excluding Placebo

Table 3 (301)

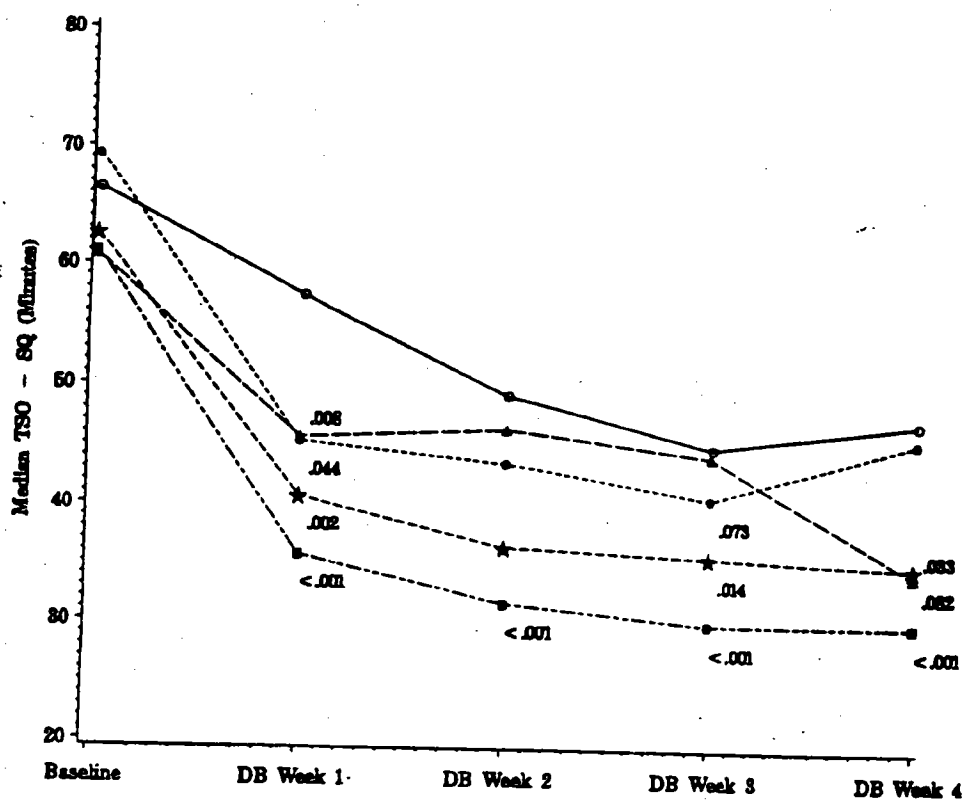
TSO (MINUTES)–ITT PATIENTS: OBSERVED VALUE ANALYSIS
SUMMARY

Study Segment	Statistic	Treatment Groups: Placebo	5 mg Zal[a]	10 mg Zal	20 mg Zal	10 mg Zolp[b]
PL Run-in	n	118	118	119	116	115
	Mean	80.42	81.53	77.69	72.45	70.54
	Median	66.43	69.29	62.50	61.07	60.71
	SD	50.86	46.74	45.91	41.51	40.39
	Minimum	24.29	18.33	20.00	19.29	24.29
	Maximum	319.29	240.00	257.14	233.33	274.29
DB Week 1	n	118	118	119	116	115
	Mean	69.78	65.21	53.87	42.49	51.93
	Median	57.50	45.36	40.71	35.71	45.71
	SD	49.13	69.29	38.47	26.63	33.75
	Minimum	10.00	8.33	10.00	10.00	8.57
	Maximum	275.00	660.00	207.86	161.25	205.00
DB Week 2	n	113	113	113	111	109
	Mean	60.53	59.41	51.65	41.37	54.73
	Median	49.29	43.57	36.43	31.67	46.43
	SD	44.27	44.35	37.87	29.28	39.54
	Minimum	10.00	7.86	7.14	9.29	10.00
	Maximum	244.29	273.83	162.86	131.43	245.00
DB Week 3	n	109	108	107	104	105
	Mean	60.62	52.90	48.20	38.10	51.83
	Median	45.00	40.71	35.71	30.00	44.29
	SD	43.70	43.70	33.81	27.42	35.39
	Minimum	11.14	6.43	8.57	5.71	8.57
	Maximum	300.00	296.57	150.00	132.86	217.14
DB Week 4	n	107	101	102	101	98
	Mean	56.44	58.87	46.54	39.47	45.21
	Median	47.14	45.63	35.00	30.00	34.29
	SD	38.79	47.50	31.41	32.64	33.40
	Minimum	9.00	3.29	9.00	6.00	7.86
	Maximum	195.00	270.83	140.00	224.29	155.71
PL Run-out	n	106	98	100	98	96
	Mean	56.45	61.15	57.40	54.08	71.13
	Median	45.00	45.00	43.33	34.17	65.00
	SD	41.77	49.90	45.40	45.59	50.18
	Minimum	5.00	4.00	8.33	6.67	10.00
	Maximum	250.00	302.50	250.00	240.00	221.67

a: Zal = Zaleplon
b: Zolp= Zolpidem

Figure 1 (301)

MEDIAN TSO OVER TIME AND COMPARISONS BETWEEN GROUPS (ITT AND OBSERVED CASES)

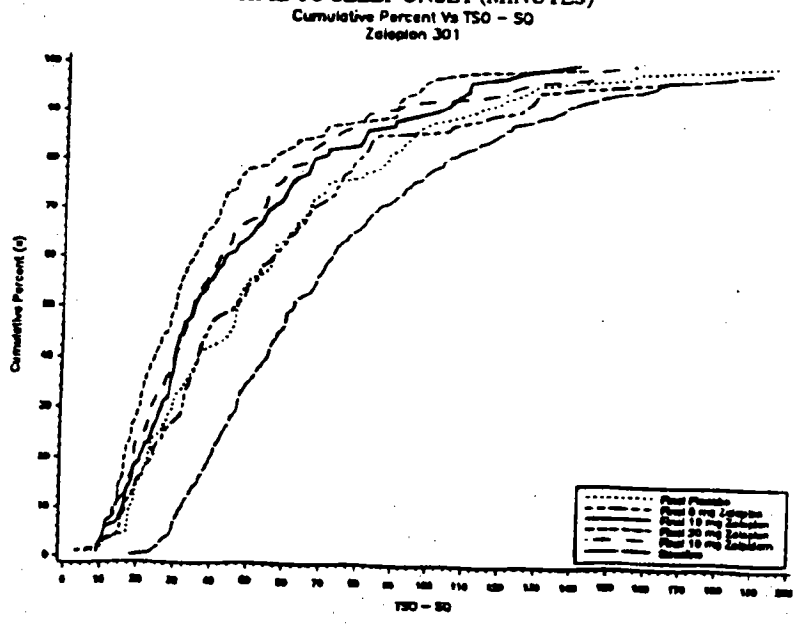


Therapy (Baseline N) Placebo (118) 5 mg Zal (118)
10 mg Zal (119) 20 mg Zal (116)
10 mg Zolp (115)

Primary comparisons of Placebo to Zaleplon are ranked Dunnett p-Value
Secondary comparisons of Placebo to Comparator are ranked ANCOVA Pairwise Contrast p-Value

Figure 2

CUMULATIVE DISTRIBUTION OF PATIENTS (301-US): TIME TO SLEEP ONSET (MINUTES)



STUDY 307

Table 1 (307)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS: ALL PATIENTS IN SAFETY ANALYSIS AND INTENT-TO-TREAT EFFICACY ANALYSIS

Characteristic	Placebo (n = 153)	Zaleplon 10 mg/10 mg (n = 242)	Zaleplon 10 mg/20 mg (n = 242)	Total (n = 637)	p-Value[a]
Sex, No. (%)					
Men	60 (39.2)	97 (40.1)	94 (38.8)	251 (39.4)	0.97[F]
Women	93 (60.8)	145 (59.9)	148 (61.2)	386 (60.6)	
Age, years					
Mean	42.4	43.3	43.0	43.0	0.66[A]
SD	11.8	11.8	11.4	11.6	
Range	19 - 65	19 - 65	19 - 65	19 - 65	
Ethnic origin, No. (%)					
Black	10 (6.5)	18 (7.4)	17 (7.0)	45 (7.1)	0.34[C]
Hispanic	1 (0.7)	8 (3.3)	11 (4.5)	20 (3.1)	
Asian		4 (1.7)	4 (1.7)	8 (1.3)	
White	134 (87.6)	202 (83.5)	208 (86.0)	544 (85.4)	
Other	8 (5.2)	10 (4.1)	2 (0.8)	20 (3.1)	
Weight, kg					
Mean	75.51	74.82	75.02	75.06	0.80[A]
SD	16.41	16.7	15.55	16.18	
Range	47.17 - 135.62	45.13 - 163.29	44.45 - 123.83	44.45 - 163.29	
Primary diagnosis, No. (%)					
Primary insomnia	149 (97.4)	232 (95.9)	230 (95.0)	611 (95.9)	0.56[F]
Insomnia- psychiatric	4 (2.6)	10 (4.1)	12 (5.0)	26 (4.1)	
Zung anxiety score					
Mean	32.8	32.7	32.4	32.6	0.48[A]
SD	6.25	5.6	5.9	5.85	
Range	23 - 49	20 - 49	22 - 50	20 - 50	
Zung depression score					
Mean	36.1	36.1	35.6	35.9	0.44[A]
SD	6.8	6.9	7.25	7.0	
Range	24 - 53	22 - 51	23 - 53	22 - 53	

[a] A = ANOVA, F = Fisher's Exact Test, C = chi-square test

Table 2 (307)

TSO (MINUTES)–INTENT-TO-TREAT PATIENTS: OBSERVED VALUE ANALYSIS (SUMMARY)

	Values	Treatment Group: Placebo	Zaleplon 10 mg/10 mg	Zaleplon 10 mg/20 mg	Zaleplon All
-7 to -1	n	153	242	242	484
	Median	68.57	63.83	64.64	64.14
	Mean	77.93	79.81	81.93	80.87
	SD	43.21	51.34	53.40	52.34
	Min	12.86	18.00	19.29	18.00
	Max	212.86	385.71	343.13	385.71
Week 1	n	153	241	242	483
	Median	49.29	39.29	42.00	40.71
	Mean	63.26	51.51	55.10	53.31
	SD	43.67	41.38	45.73	43.60
	Min	12.86	2.43	7.50	2.43
	Max	225.00	235.71	310.00	310.00
Week 2	n	145	232	229	461
	Median	50.00	35.00	34.29	35.00
	Mean	63.22	50.09	48.25	49.18
	SD	46.07	43.92	44.30	44.07
	Min	10.00	3.43	5.00	3.43
	Max	252.00	390.00	417.50	417.50

Table 3 (307)

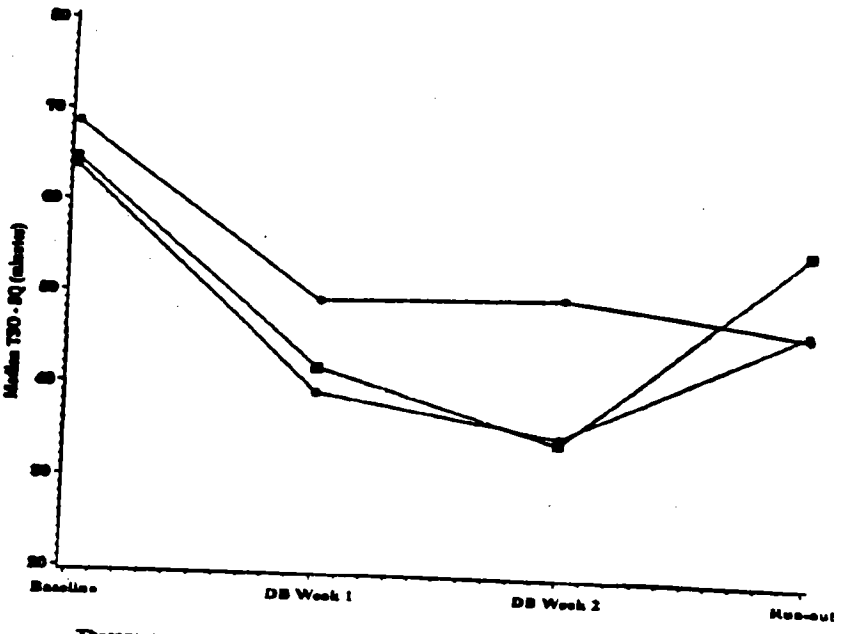
TSO (MINUTES)–INTENT-TO-TREAT PATIENTS: OBSERVED VALUE ANALYSIS FOR THE 10 mg DOSE OF ZALEPLON - WEEK 1

Study Period	Treatment Group	Number of Patients	Median	p-Value Difference from Zaleplon
Days -7 to -1	Placebo	153	68.57	
	Zaleplon[a]	484	64.14	
DB Week 1	Placebo	153	49.29	<0.001
	Zaleplon	483	40.71	

a: Intent-to-treat patients from both zaleplon treatment groups were combined for the analysis for the treatment conditions of 10 mg zaleplon.

Figure 1 (307)

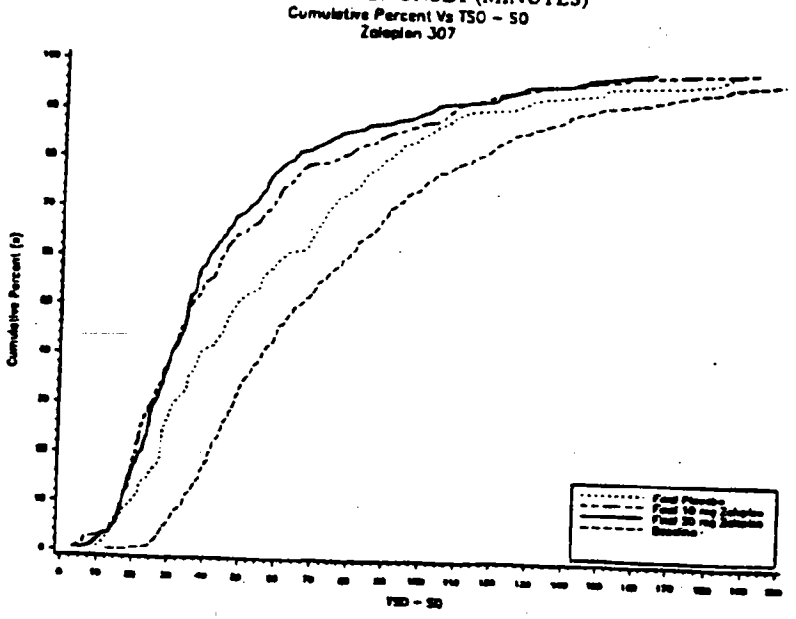
MEDIAN TIME TO SLEEP ONSET: INTENT-TO-TREAT POPULATION



Number of Patients:				
Placebo	153	145		
Zal 10 mg/10 mg	242	241	139	
Zal 10 mg/20 mg	242	242	232	139
			229	224
				226

Figure 2 (307)

FIGURE 3.1.2.1.1A. CUMULATIVE DISTRIBUTION OF PATIENTS (307-US/CA): TIME TO SLEEP ONSET (MINUTES)



STUDY 303

Table 1 (303)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR PATIENTS IN ITT POPULATION

Characteristic	ZAL 05 MG (N=113)	ZAL 10 MG (N=112)	ZAL 20 MG (N=116)	ZOL 10 MG (N=115)	PLACEBO (N=118)	p-value
AGE (YEARS), N	113	112	116	115	118	
MEAN	42.5	42.6	42.6	44.3	42.1	0.683 (A)
STANDARD DEVIATION	12.9	12.5	12.2	12.5	12.0	
RANGE	20 - 65	18 - 66	19 - 67	18 - 65	22 - 65	
SEX, N(%)						
FEMALE	66 (58%)	72 (64%)	81 (70%)	77 (67%)	74 (63%)	0.446 (B)
MALE	47 (42%)	40 (36%)	35 (30%)	38 (33%)	44 (37%)	
ETHNIC ORIGIN, N(%)						
BLACK					1 (1%)	1.000 (B)
ORIENTAL (ASIAN)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	
WHITE	112 (99%)	111 (99%)	115 (99%)	114 (99%)	116 (98%)	
WEIGHT (KG), N	113	112	116	115	117	
MEAN	68.1	67.4	67.7	68.7	68.3	0.961 (A)
STANDARD DEVIATION	14.3	14.5	11.4	13.1	15.9	
RANGE	44 - 125	0 - 109	44 - 106	48 - 107	39 - 140	
PRIMARY DIAGNOSIS, N(%)						
INSOMNIA	113 (100%)	112 (100%)	116 (100%)	115 (100%)	118 (100%)	
ZUNG ANXIETY, N	113	112	116	115	118	
MEAN	36.3	36.6	36.2	36.1	36.4	0.984 (A)
STANDARD DEVIATION	6.7	6.3	6.7	6.2	6.4	
RANGE	23 - 49	23 - 49	23 - 49	22 - 49	22 - 49	
ZUNG DEPRESSION, N	113	112	116	115	118	
MEAN	38.7	37.8	38.2	37.4	38.3	0.683 (A)
STANDARD DEVIATION	6.6	7.0	8.7	6.5	6.2	
RANGE	25 - 49	23 - 51	24 - 93	24 - 52	24 - 49	

NOTE: (A) ANALYSIS OF VARIANCE WITH TREATMENT AS FACTOR.
(B) FISHERS EXACT TEST

Table 2 (303)

TIME TO SLEEP ONSET (minutes) - ITT POPULATION - 1 CENTRE EXCLUDED-

OBSERVED CASES ANALYSIS

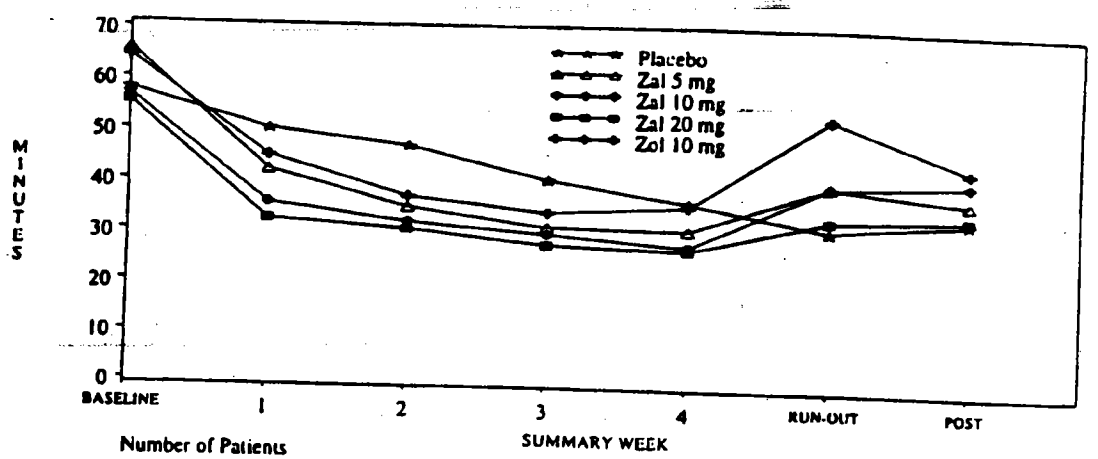
Summary Week	Placebo	Zaleplon 5	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg
Baseline	n=118	n=113	n=112	n=116	n=115
Median	58	66	57	55	64
IQR [a]	41.3-85.0	47.1-97.1	42.5-98.0	41.1-86.2	47.9-90.7
Week 1	n=118	n=113	n=112	n=116	n=114
Median	50	42	36	33	45
IQR	30.0-81.4	25.7-66.3	23.6-68.6	22.7-48.9	30.0-61.4
p-value Dunnett's test		0.014	0.001	<0.001	
p-value ANCOVA		0.005	<0.001	<0.001	0.047
Week 2	n=115	n=110	n=110	n=113	n=110
Median	47	35	32	31	37
IQR	27.1-70.7	21.4-60.0	22.9-55.7	20.0-42.9	25.0-57.1
p-value Dunnett's test		0.006	0.003	<0.001	
p-value ANCOVA		0.002	0.001	<0.001	0.006
Week 3	n=113	n=102	n=104	n=108	n=105
Median	41	31	30	28	34
IQR	22.9-68.6	20.0-55.0	21.4-50.7	17.5-42.4	23.3-47.1
p-value Dunnett's test		0.010	0.010	<0.001	
p-value ANCOVA		0.004	0.004	<0.001	0.043
Week 4	n=107	n=102	n=99	n=103	n=100
Median	36	31	28	27	36
IQR	20.8-57.5	18.6-60.0	20.0-45.0	17.1-40.0	23.2-49.5
p-value Dunnett's test		0.22	0.028	0.006	
p-value ANCOVA		0.093	0.010	0.002	0.54
Run-out	n=104	n=100	n=95	n=99	n=95
Median	31	40	40	33	53
IQR	20.0-60.0	20.0-73.3	21.7-70.0	16.7-55.0	26.7-90.0
p-value Dunnett's test		0.70	0.32	1.00	
p-value ANCOVA		0.37	0.14	0.99	0.003
Post-Study	n=101	n=94	n=94	n=98	n=97
Median	34	38	41	34	44
IQR	20.0-52.5	18.8-78.8	23.8-67.5	21.3-56.3	23.8-78.3
p-value Dunnett's test		0.84	0.18	0.94	
p-value ANCOVA		0.50	0.076	0.64	0.13

a: IQR = interquartile range

Figure 1 (303)

Median Time to Sleep Onset

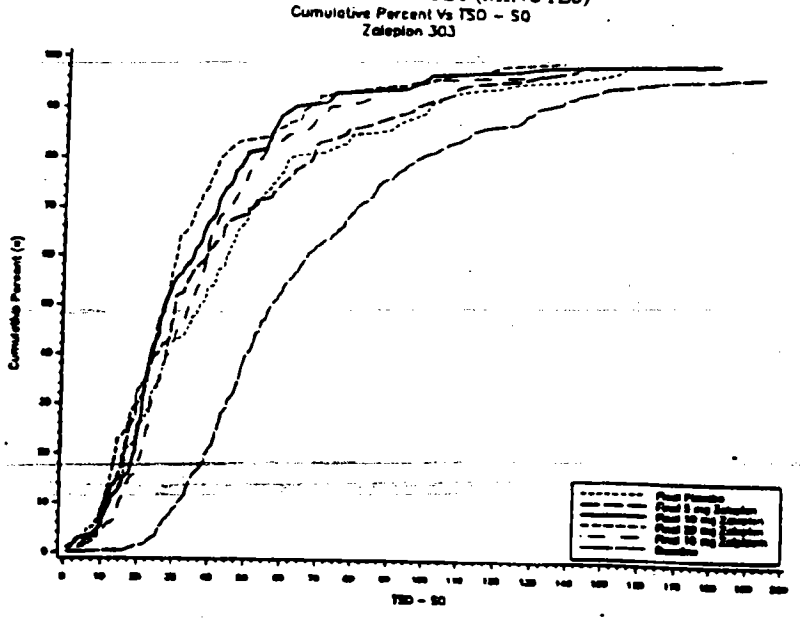
Intent-to-Treat Population



Group	Number of Patients						
Placebo	118	118	115	113	107	104	101
Zaleplon 5 mg	113	113	110	102	102	100	94
Zaleplon 10 mg	112	112	110	104	99	95	94
Zaleplon 20 mg	116	116	113	108	103	99	98
Zolpidem 10 mg	115	114	110	105	100	95	97

Figure 2 (303)

FIGURE 3.1.2.1.1E. CUMULATIVE DISTRIBUTION OF PATIENTS (303-EU/CA): TIME TO SLEEP ONSET (MINUTES)



STUDY 306

Table 1 (306)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR PATIENTS IN ITT POPULATION
DOUBLE BLIND TREATMENT PHASE

CHARACTERISTICS	ZAL 10 MG (N=145)	ZAL 5 MG (N=139)	PLACEBO (N=138)	p-VALUE
AGE (YEARS), N	145	139	138	
MEAN	72.5	72.5	72.4	0.976 (A)
STANDARD DEVIATION	6.3	5.9	6.8	
RANGE	64 - 91	59 - 90	63 - 95	
SEX, N				
FEMALE	104 (72%)	87 (63%)	94 (68%)	0.251 (B)
MALE	41 (28%)	52 (37%)	44 (32%)	
ETHNIC ORIGIN, N				
BLACK		1 (1%)	1 (1%)	0.548 (B)
WHITE	145 (100%)	138 (99%)	137 (99%)	
WEIGHT (KG), N	145	139	138	
MEAN	68.9	68.5	67.6	0.639 (A)
STANDARD DEVIATION	11.4	10.9	11.8	
RANGE	40 - 103	45 - 97	42 - 96	

NOTE: (A) ANALYSIS OF VARIANCE
(B) FISHERS EXACT TEST

Table 2 (306)

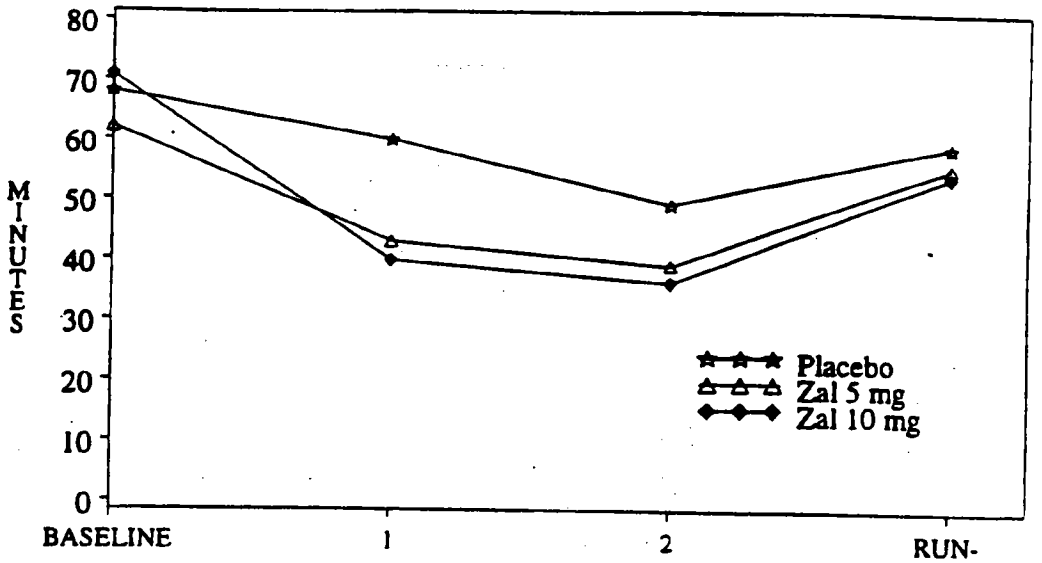
TIME TO SLEEP ONSET (minutes) - ITT POPULATION :
RANKED OBSERVED-VALUE ANALYSIS

Summary Week		Placebo	Zaleplon 5 mg	Zaleplon 10 mg
Baseline	Number of patients	N = 138	N = 139	N = 145
	Median	68.0	62.1	70.7
	IQR	45.0 - 107.1	48.6 - 85.7	46.4 - 102.9
Week 1	Number of patients	N = 137	N = 139	N = 145
	Median	60.0	43.1	40.0
	IQR	35.7 - 85.8	25.7 - 65.7	25.7 - 67.9
	p-Value Dunnett's test		0.001	< 0.001
Week 2	Number of patients	N = 136	N = 129	N = 139
	Median	49.3	39.3	36.4
	IQR	30.0 - 85.4	21.0 - 57.5	22.5 - 57.9
	p-Value Dunnett's test		< 0.001	< 0.001
Run-out	Number of patients	N = 131	N = 129	N = 137
	Median	59.3	55.7	54.3
	IQR	30.0 - 90.0	34.3 - 75.0	35.0 - 90.0
	p-Value Dunnett's test		0.97	0.90

Figure 1 (306)

Median Time to Sleep Onset

Double Blind Intent-to-Treat Population



Group	Number of Patients			
Placebo	138	137	136	131
Zaleplon 5 mg	139	139	129	129
Zaleplon 10 mg	145	145	139	137

Figure 2 (306)

CUMULATIVE DISTRIBUTION OF PATIENTS (306-US):
TIME TO SLEEP ONSET (MINUTES)