Stat

Statistical Review and Evaluation

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NDA #: 19-908/Drug Class 1C

Applicant: Lorex Pharmaceuticals

Name of Drug: Stilnox (zolpidem tartrate)

Indication: Sleep disorders

Documents Reviewed: Volumes 1.235 - 1.239 and 1.244 - 1.258 dated February 1, 1989.

Clinical Input: David Collins, M.D (HFD-120)

I. Background:

This submission contains the results of 4 studies of the efficacy of **zolpidem** as an hypnotic compound as compared to placebo.

1. Introduction

Persons sleeping in a sleep laboratory for the first time experience insomnia known as the "first night effect. This effect results in a longer latency to persistent sleep, decreased sleep efficiency, more awakenings and decreased percentage of REM than that seen in subsequent nights. The objectives of this study were : 1) To compare the efficiency of the zolpidem 7.5 and 10 mg doses with placebo in subjects with insomnia, 2) To determine how well zolpidem is tolerated and 3) To evaluate the dose-related effects of zolpidem (5,7.5,10,15 and 20 mg).

This was a two center, single night, double-blind, randomized, parallel group study of zolpidem. In keeping with the emphasis on the 7.5 and 10 mg dose comparisons with placebo, an unbalanced randomization was employed.

2. Study Conduct:

Study Population

Healthy volunteers (Male and Female) aged 21 to 60 years with normal sleep having not previously slept in a sleep laboratory, were included in the study. The volunteers included in this study had usual sleep duration of six hours or more and sleep latency of 30 minutes or less. Subjects reported to the sleep laboratory at least one hour before a pre-established bed time. Subjects completed a questionnaire, had vital signs measured and electrodes applied for polysomnography (PSG). Medication was administered 30 minutes before bedtime. Subjects were kept awake until bedtime when they were escorted to bed, lights were turned out and the polysomnographic recording was begun. The recording continued until eight hours later when subjects were awakened, vital signs were taken and electrodes were removed. Each subject then completed the morning questionnaire, the Digit Symbol Substitution Test (DSST) and the Symbol Copying Test (SCT). Before leaving the laboratory each subject was given a questionnaire to be completed later that day and mailed to the laboratory.

Measures of Effectiveness:

The evening questionnaire collected information about the activities of the preceding 24 hours which might influence the study night's sleep. The morning questionnaire sought the subject's assessment of the night's sleep and of his or her alertness and ability to concentrate in the morning. Polysomnographic records were scored without knowledge of treatment according to methods developed by

Measures of Safety

All spontaneous reports and observed effects considered to be adverse events were recorded. Safety was assessed by collection of adverse events and a review of vital signs and clinical laboratory test results.

Sponsor's Analysis

The sponsor enrolled 595 subjects for this study, 133 were dropped prior to receiving study drug and the available data set consisted of 462 subjects with normal sleep of 6 or more hours of sleep and sleep latency of 30 minutes or less. The primary sleep variables as measured by EEG were: 1. Sleep efficiency (Total sleep time/time in bed): 2. Latency to persistent sleep (time from the beginning of the recording to the onset of the first 10 minutes of consecutive sleep): 3. Wake time during sleep; 4. Number of awakenings; 5. Percentage of sleep time in each sleep stage (I,II,III-IV and REM)

Distribution of Subjects

	# enrolled	Placebo	5 mg	7.5 mg	10 mg	15 mg	20 mg	Total
Ruth	307	52	27	52	52	26	26	235
Vogel	288	50	25	50	52	25	25	227
	595	102	52	102	104	51	51	462

The sponsor carried out the primary analysis on the available data set. The sponsor's baseline comparisons of the treatment groups (Placebo, 5 mg,7.5 mg,10 mg, 15 mg and 20 mg) with respect to gender,race, age, weight,height did not show significant differences. The sponsor has employed natural logarithmic and logit transformations to make the data symmetric and analyses of the logit of sleep efficiency, that is logarithm of p/1-p, where p=Total sleep time/time in bed and the logarithm of latency to persistent sleep and subjective latency are used in all analyses of latency and efficiency.

Primary Efficacy Analysis

Latency to persistent sleep: Table 1 gives the means and S.D's of latency to persistent sleep by treatment group. The sponsor analyzed the logarithms of latency by means of an **analysis of variance model** and found significant differences among the six treatments. The non-parametric test by the sponsor confirmed these significant differences among treatments ($p = 0.0054$). The polysomnographic recording showed that mean latencies for the zolpidem 7.5 mg and 10 mg doses were 17.0 and 17.4 minutes respectively. These were significantly shorter ($p < 0.005$) than the placebo mean. The sponsor found no significant investigator by treatment interaction ($p = 0.2611$). The sponsor did a linear regression analysis, utilizing data from all the dose groups for determining dose relationship between sleep latency and zolpidem dose and found that the overall relationship between sleep latency and zolpidem dose was **quadratic ($p = 0.0034$).** The sponsor found that latency to persistent sleep decreased with dose up to the 10mg dose and thereafter slightly increased with the 15 and 20 mg doses. There was no significant treatment by investigator interaction ($p = 0.4543$).

Sleep Efficiency: Sleep efficiency as measured by a polysomnogram is total sleep time divided by time in bed. Table 2 gives the means and S.D's of sleep efficiencies (%) by treatment group. The sponsor found that there were significant differences among the six treatment means ($p < 0.001$) for the transformed efficiency data (i.e., the logit of efficiency) and the non-parametric test confirmed the above findings.

The sleep efficiencies were significantly greater for subjects receiving zolpidem 7.5 and 10 mg than subjects receiving placebo. There was no significant investigator by treatment interaction (p = 0.266). Overall, sleep efficiencies changed in a **quadratic** fashion with dose (p= 0.0015).

Total Sleep Time: **Table 2(a)** gives the mean and S.D of Total Sleep Time (Mins) by treatment group. The analysis of variance of Total sleep time showed significant differences among treatment means (p = 0.009) and the non-parametric test (p = 0.0001) confirmed this finding. The zolpidem 7.5 and 10 mg doses significantly increased the Total sleep time as compared to placebo. There is no treatment by investigator interaction effect. Overall, the total sleep time changed in **quadratic** fashion with dose (p = 0.0047). Total sleep time increased up to 10 mg dose and then decreased slightly with the 15 and 20 mg doses.

Sleep Maintenance: Table 3 gives the treatment means for the polysomnograpic recordings of wake time during sleep. The zolpidem 7.5 and 10 mg doses significantly reduced wake time. There was no significant investigator by treatment interaction (p = 0.4561). Overall, the dose relationship with wake time was linear and the slope was significantly different (p = 0.004) from zero. **Table 4** gives the mean and S.D of number of awakenings for the treatment groups. The zolpidem dose 7.5 mg and 10 mg significantly reduced the polysomnographic number of awakenings as compared to placebo. There is no treatment by investigator interaction effect (p=0.9024).

Sleep Staging: **Table 5** gives the mean sleep stages(Q). The analysis of variance indicated statistically significant treatment effects on the percentage of stage 3-4 and REM sleep in relation to total sleep time. There was a significant increase in the % of stage 3-4 sleep and decrease in the percent of REM sleep at the 7.5 mg dose compared to placebo group. A significant decrease in the percent of REM sleep was also seen at the 10 mg dose. The relationship between stage 3-4 sleep and dose was linear and the slope was significantly (p = 0.01) different from zero. The relationship between the percent REM and dose was also linear and the mean slope was significantly different (p < 0.001) from zero.

Tables 6 and 6(a) give the Absolute REM sleep (mins) and Latency to REM sleep (mins). Absolute REM sleep was 81.0 and 81.5 minutes for subjects in the 7.5 and 10 mg dose groups, 7-8 minutes less than on placebo (p < 0.04).

Secondary Efficacy Variables

The sponsor assessed the sleep inducing effect of zolpidem by the morning questionnaire. **Table 7** gives the **Perceived (Subjective) sleep latency** (Mins.). Results of the logarithm of perceived latency were used in determining the overall drug effect and pair-wise comparisons were restricted to the placebo versus 7.5 and 10 mg treatment groups. Perceived latencies with zolpidem 7.5 and 10 mg doses were significantly shorter than

that of placebo. **Table 8** gives the mean and S.D of **ease of falling asleep.** The 7.5 and 10 mg zolpidem dose groups reported significantly greater ease in falling asleep ($p < 0.001$). Sleep efficiency was also measured by the morning questionnaire. **Table 9** gives the **Subjective total sleep time (Hours).** Mean subjective sleep times for the 7.5 and 10 mg treatment groups were significantly different.

Quality of Sleep: **Tables 10 (a) and 10(b)** give the means and standard deviations of **sleep quality** and **refreshing quality of sleep** as measured by the morning questionnaire. The 7.5 and 10 mg treatment groups experienced a significantly better quality of sleep than placebo. No significant overall treatment difference was observed with respect to the refreshing quality of sleep as compared to placebo ($p = 0.0825$).

Safety Variables

Psychomotor Performance: Performance tests assessing psychomotor function included the **Digital Symbol Substitution Test (DSST)** and **Symbol Copying Test (SCT).** The number of symbols copied for both the tests were analyzed. Overall, there were no significant differences between the 7.5 and 10 mg dose groups and placebo.

The morning questionnaire asked the subject to describe his/her ability to concentrate. There were no significant differences between the zolpidem 7.5 and 10 mg groups and the placebo group. Morning sleepiness was evaluated using a visual analog scale (0 = not at all sleepy to 100 = very sleepy). There were no significant differences between placebo and zolpidem 7.5 and 10 mg on the perception of sleepiness in the morning, although the 10 mg comparison was suggestive of an effect ($p = 0.1559$ and $p = 0.0511$, respectively). A visual analog scale was used to evaluate "drugged feeling". The 7.5 and 10mg treatment groups were not significantly different from placebo ($p = 0.9129$ and $p = 0.4036$).The proportion of subjects who felt sleepy during the day after treatment was determined by the response to the main-in-questionnaire. There were no significant differences between the 7.5 and 10 mg doses and placebo.

Efficacy Results by Investigator:

Each site's data was analyzed separately. At Dr.Vogel's site, significant increases in sleep efficiency and total sleep time and decrease in latency to persistent sleep were noted for both the 7.5 and 10 mg doses in comparison with placebo. With respect to the secondary sleep variables, significant differences from placebo were observed for wake time during sleep and percentage of REM sleep significantly decreased with 7.5 mg only. At Dr.Roth's site significant increases in sleep efficiency were observed for both zolpidem doses 7.5 mg and 10 mg in comparison with placebo; but significant increase in total sleep time was observed for only 10 mg. For latency to persistent sleep, zolpidem dose of 10 mg only showed a

significant decrease (p = 0.028) in comparison with placebo.
With respect to the secondary sleep variables, decrease in the percentage of REM sleep was significant for both 7.5 and 10 mg doses from placebo.

Multiple Comparison Analyses: Table 11 summarizes the results of the Tukey-Kramer test of treatment means in the analysis of the primary sleep parameters. Latency to persistent sleep was significantly shorter in the 7.5, 10 and 15 mg zolpidem groups than in the placebo group. The reduction in subjective latencies in each of the 10, 15 and 20 mg dose groups was significantly greater than that of placebo, 5 or 7.5 mg doses. Significantly fewer awakenings were seen with 7.5 and 20 mg doses than on placebo. The percentage of REM was significantly less on all doses than on placebo. percent REM was also significantly less after 20 mg dose than after 10 mg dose.

Evaluable Data Set: This data set excluded 24 (5.2%) subjects who had major protocol violations. Results from the analysis of evaluable subject data were similar to those of the analysis of all available subjects. The only treatment difference between the two data sets was the absence of a significant change in the percentage of stage 3-4 sleep in the evaluable data set.

Safety Evaluation

Adverse Events: Seventy-one events occurred in 47 subjects during the treatment period. The sponsor states that none of these events were clinically serious, nor did any of them cause a subject to fail to complete the treatment period. The proportion of subjects with adverse events differed significantly ($p < 0.001$) across the treatment groups. No significant differences ($p > 0.340$) between the 5, 7.5 or 10 mg zolpidem dose groups and placebo with respect to the proportion of subjects having adverse events were noted. The proportion of subjects experiencing adverse events in the 20 mg group (31.4%) was significantly higher ($p < 0.001$) than the corresponding proportion for the placebo group (7.8%).

Reviewer's Evaluation and Conclusions

The sponsor's analyses have indicated the following: The latency to persistent sleep as assessed by the polysomnograph for both the 7.5 and 10 mg treatment groups was significantly shorter than for the placebo group. The subjective sleep latency for these two treatment groups was also significantly shorter than for placebo. Sleep efficiency increased significantly from 88% in the placebo group to 92% in both the 7.5 and 10 mg zolpidem groups, so also Total sleep time and Sleep quality, as judged by the subjects, were significantly improved ($p=0.0002$ and $p=0.0001$ respectively) by both treatments. The sponsor's results suggest that these improvements in sleep latency, efficiency, total sleep time and

quality were achieved without evidence of residual effects or increased daytime sleepiness. Doses of 7.5 and 10 mg zolpidem had no effect on the perception of sleepiness in the morning. The sponsor's analysis shows that both sleep latency and sleep efficiency exhibited a quadratic relationship to dose, in that the best effects were noted at 7.5 mg and 10 mg. The incidence of adverse events was also dose related. The sponsor noted a marginally significant difference (p=0.069) between the 15 mg group (where 17.6% experienced adverse events) and the placebo group. The proportion of subjects experiencing adverse events in the 20 mg groups (31.4%) was significantly higher (p<0.001) than the corresponding proportion for the placebo group (7.8%).

The **sponsor** has done appropriate statistical analyses of both Primary and Secondary Efficacy Variables and the **reviewer's independent statistical analyses** are in agreement with the sponsor's analyses quoted above. The results of this double-blind, single night, randomized, parallel study of zolpidem 5, 7.5, 10, 15 , 20 mg and placebo with emphasis on 7.5 mg and 10 mg dose comparisons with placebo have shown statistical evidence of superiority of both the 7.5 and 10 mg doses to placebo for all primary efficacy variables.

III LSH Dose-response study of the effect of zolpidem on Insomnia produced by 3-Hour phase advance

This was a single-center, randomized, double-blind, placebo-controlled sleep laboratory study composed of two independent 3 period crossovers in healthy adults without insomnia as follows:

Crossover I	Placebo, Zolpidem 10 mg and 20 mg
Crossover II	Placebo, Zolpidem 5 mg and 15 mg

The 3 treatments within each crossover were tested in **three** separate periods (Period 1, 2, and 3). Five to ten days separated each study period. Each study period consisted of two study nights. On Night 1, each subject received placebo 30 minutes before his/her **usual bedtime**. On Night 2, the bedtime and study drug (placebo or zolpidem) administration were **advanced 3 hours** compared to Night 1.

Study Conduct

1. Study Population

Subjects aged 18 to 60 were screened to ensure good health. Following a physical examination and a medical and sleep history,subjects had two consecutive nights of polysomnographic (PSG) evaluation to rule out various sleep disorders and to document normal sleep. Night 1 was the usual bedtime/placebo while night 2 was the 3-hour advance bedtime/drug.

The drugs tested during night 2 were placebo and the zolpidem doses. Polysomnnography began at bedtime and continued for approximately 480 minutes. Assessments in the morning after night 1 and 2 included vital signs, a morning questionnaire and the symbol copying digital symbol substitution tests. On the morning following the advanced night, subjects underwent two sleep latency tests. Each subject who met all entry criteria was randomly assigned to one of the two crossovers and to a sequence of treatment periods within that crossover.

2. Measures of Effectiveness

Efficacy was evaluated objectively by polysomnography and subjectively by morning questionnaires. The morning questionnaire assessed the subject's evaluation of the night's sleep, including measures of indication and maintenance and of his/her alertness and ability to concentrate.

3. Measures of Safety

All reports and observed effects considered to be adverse events were recorded. Safety was assessed by recording of adverse events and a review of vital signs and clinical laboratory test results.

4. Sponsor's Analysis

The sponsor enrolled 53 subjects for this sleep study; 34 were randomized to treatment and of these 31 completed the 3-period study (mean age = 24), with 15 in crossover I and 16 in crossover II. The evaluable data set (n=34) included all the patients with normal sleep who completed a 3-hour phase advance. Since normal baseline sleep and the three hour phase advance were prerequisites for this model of insomnia, the sponsor used the evaluable data set for the primary analysis. Table 12 shows the descriptive statistics for the combined placebo groups for the 2 crossover treatment means (standard deviations). Although the mean sleep efficiency during placebo phase advance was 85%, 16 of the 29 subjects (six in crossover I and 10 in crossover II) were not affected since they had efficiencies ≥ 90%. **Latency to persistent to sleep** is the amount of time from bedtime until the start of 10 consecutive minutes of sleep. Table 13 gives the descriptive statistics for the variable latency to persistent sleep. The two placebo means (25 and 13 minutes) seem dissimilar, but do not differ significantly (Table 13: $p = 0.602$). The 25 minute mean is mostly due to patient 24's latency of 140 minutes. This latency also increased variance. The sponsor did ANOVA of the logarithm of sleep latency and found that the three treatments in both of the crossovers did not differ significantly (Table 13: $p = 0.834$ and 0.152). But ANOVA on ranks showed significance in crossover II and multiple comparisons showed that the latency for 15 mg was less than placebo. The sponsor's analysis also indicated that neither period nor sequence effects were significant. The sleep inducing effect of zolpidem was evaluated subjectively by a morning questionnaire and it was found that

5 mg and 15 mg attained significance (p-value = 0.055) on subjective latency and 10 mg, 15 mg and 20 mg, improved the ease of falling asleep significantly. **Sleep efficiency** is total time divided by time in bed. Changes in sleep efficiency are the results of changes in total sleep time. The results of **ANOVA** of logit of efficiency **(Table 14)** showed that although there were no indications of significant differences in crossover I (though both 10 mg and 15 mg treatment efficiencies were higher than that of placebo), the treatments (placebo, 5 mg and 15 mg) exhibited significant differences (p value = 0.034) and Scheffe multiple comparisons indicated that the 5 mg and 15 mg treatments significantly increased efficiency compared to placebo. In the analysis of logit of efficiency, neither period nor sequence effects were significant.

The analysis of subjective sleep duration (minutes) **(Table 15)** showed that, within each crossover, the treatments differed significantly and the mean sleep times for the 10 mg, 15 mg and 20 mg treatments were significantly greater than the means for placebo. In general, 5 mg, 10 mg and 15 mg of zolpidem improved numerically PSG sleep efficiency beyond placebo; 5 mg and 15 mg were significantly different from placebo **(Table 14).** The phase advance produces more of an effect on sleep efficiency in the first half of the night and this was indicated by the improved efficiency of 88% in the last half as compared to the efficiency of 82% in the first half of night 2 after placebo. The 5 mg, 10 mg and 15 mg doses had a significantly higher sleep efficiency than placebo during first half of the phase advanced nights. The 10 mg and 20 mg doses significantly reduced the polysomonogrphic recordings of wake time during sleep **(Table 16).** With respect to the number of awakenings, there were no significant differences among treatments in either of the crossovers (p = 0.431 and 0.712) **(Table 16).**

However, the subjective analysis of the morning questionnaire (Question 3: the amount of time they spent awake after falling asleep) showed that 10 mg, 15 mg, and 20 mg treatments significantly reduced the perceived awake time after sleep was initiated **(Table 16).** The 5 mg and 15 mg treatments significantly improved the perceived quality of sleep compared to placebo **(Table 16).** On the morning of the advanced night, subjects underwent two sleep latency tests, one and three hours after the nighttime polysomnographic recording was terminated. In the analysis of Latency Test 1, there was a significant difference among the treatments within crossover II and latency for the 15 mg treatment was significantly shorter than that of placebo.

The symbol copying test (SCT) and the digit substitution test (DSST) were administered on the mornings after nights 1 and 2. In the analysis of crossover I's DSST, there was an indication (p = 0.083) of treatment differences, but there were no significant treatment differences in crossover II (p > 0.15). Subjective analysis on the morning questionnaire (Question 10: Describe you ability to concentrate) showed no significant differences among treatments in either crossover. Performance tests did

not indicate any evidence of residual effects in the morning following administering of zolpidem.

Few adverse events were reported. No adverse events were serious or resulted in a subject's withdrawal from the study.

Reviewer's Evaluation and Conclusions:

This single center, double-blind, randomized trial actually consisted of 2 independent 3 treatment, 3 period crossover studies, each utilizing placebo plus 2 doses of zolpidem. Since the overall variability of the observations within Crossover I generally exceeded that of Crossover II, the sponsor thought that it would be reasonable to analyze the two crossovers separately. It may be pointed out here that larger variability in Crossover 1, as well as the smallness of the sample size (n=15), might have contributed to the lack of significance among the treatments, Placebo, 10 mg and 20 mg. Overall, randomization procedures followed seem reasonable. The sponsor has carried out correctly the mechanics of analyses, be they parametric or non-parametric. The use of transformations, such as natural logarithm of latency of logit of efficiency to overcome the variability and skewness characteristics during placebo treatment, is convincing. The reviewer did an independent analysis of the latency to persistent sleep, using a distribution-free test for ordered alternatives
and found that his findings supported the sponsor's claim of significant differences among the three treatment groups, placebo, zopidem 5 mg and 15 mg, using **ANOVA** on ranks. Thus, the reviewer's analyses of the efficacy and safety variables corroborated the claims of the sponsor that zolpidem demonstrated efficacy of the variables, polysomnographic sleep efficiency, subjective total sleeep time, ease of falling sleep an quality of sleep at 5 mg and 15 mg, inspite of the fact that efficiencies during placebo treatment remained in excess of **90%** for the majority of subjects.

IV LSH Zolpidem in Insomniacs

insomnia is defined as the complaint for more than one month of disturbed or unrefreshing sleep with a wake time consequence. The objectives of this study were: 1) to evaluate the effect of 10 mg and 15 mg of zolpidem versus placebo when given to insomniacs; 2) to determine whether patients develop tolerance to the hypnotic effect of zolpidem when given for 30 consecutive nights; 3) to evaluate sleep following abrupt discontinuation of zolpidem after 35 consecutive nights of treatment.

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled and parallel group study in outpatients with insomnia. Following four nights of screening each patient was randomly assigned to one of three treatment groups, zolpidem 10 mg, 15 mg or placebo. Patients then entered the seven-week study. The first week was a single-blind

placebo period, during which baseline data were obtained. Dur[illegible] the next five weeks the patients received their randomized treatment. The seventh week was actually a three-night period during which patients received single-blind placebo. Patients were evaluated in the sleep laboratory during the first two nights of the placebo week, the first two nights of weeks 2-6, and all three nights of week 7. On the remaining nights of weeks 1-6, patients took their assigned medication at home.

Measures of Effectiveness: Efficacy was evaluated objectively by means of polysomnographic recordings obtained during the first two nights of each week of the treatment period. The primary efficacy parameters specified in the protocol were latency to **persistent sleep, sleep efficiency (total sleep time) and wake time after sleep from polysomnographic recordings.** Efficacy was evaluated subjectively by the **Morning Questionnaire** and by a **Modified Global Impressions Scale** was completed once at the end of the five weeks of double-blind treatment.

Performance Tests: During the morning of the first two days of each study week, patients undertook a **DSST** and **DSCT** to assess residual effects.

Total enrolled	178
Not meeting inclusion criteria	103

	Placebo	10 mg	15 mg	Total
Randomized to treatment	24	26	25	75
Discontinued during double-blind treatment	-1	-4	-3	-8
Completed double blind treatment	23	22	22	67

Data Sets for Analysis: All patients who received medication had some follow-up data and are included in both the intent-to-treat and evaluable data sets. The **intent-to-treat** data set was used in the **sponsor's analysis.**

Data Set	Placebo	10 mg	15 mg	Total
Intent-to treat	24	26	25	75
Evaluable	24	26	25	75
Completers	23	22	22	67

Patient Characteristics: The treatment groups were tested for comparability with respect to **sex, race, age, weight, height, sleep history and number of patients with previous hypnotic.** There were no significant differences among treatment groups for these characteristics

Baseline Characteristics: Baseline values of the efficacy variables were collected after randomization, during the single-blind placebo period. Sleep efficiency differed significantly among treatment groups at baseline; the 10 mg group had higher efficiency **(85.3%)** than either the placebo group **(80.8%)** or the 15 mg group **(80.6%).** There were no significant treatment differences on any morning questionnaire items or on the mean **DSST/DSCT** scores at baseline.

1. Efficacy Results

Sleep Induction: The primary measure of sleep induction in this study was latency to persistent sleep from the **PSG.** The effect of zolpidem on latency to persistent sleep was manifest within the first week of treatment and maintained throughout the study. **Table 17** gives the mean and standard deviation of the **Latency to persistent sleep** for baseline and all subsequent weeks for the three treatment groups. The latency was significantly shorter in the 15 mg group than in the placebo group at weeks 2 through 6 (the active treatment period) as well as at end point (each patient's last available treatment visit). The 10 mg group showed similar improvement, although the difference from the placebo group was not significant at week 6 or end point. The three treatment groups did not differ significantly at baseline or during the post treatment week.

A secondary analysis of treatment effect on latency to persistent sleep was based on the change from baseline (week 1). **Table 18** gives the mean and standard deviation of **change in latency to persistent sleep (mins.) from baseline (week 1).** All weeks showed decreased sleep latency compared with baseline for both treatment groups. The decrease was significantly greater in the 15 mg group than the placebo group at weeks 2, 3, 4 and 6 and at endpoint. Improvement in sleep latency for the 10 mg group did not differ significantly from that of placebo except at week 7 (post treatment). The decrease in latency was significantly greater in the 15 mg group than in the 10 mg group at weeks 2 and 6 and at endpoint. **Subjective sleep latency** from the morning questionnaire supported the results of polysomnography. **Table 19** gives the mean and standard deviation of subjective sleep latency (min). Subjective latency was significantly shorter in the 15 mg group than in the placebo group at every week during double blind treatment. The 10 mg group had numerically shorter latencies than the placebo group at all weeks. These differences reached significance at weeks 3, 4 and 5 and showed trends toward significance at week 6 and at end point. A visual analogue scale measured ease of falling asleep. Throughout the double blind treatment period (except at week 3, the 15 mg mean was significantly lower than the placebo group mean, i.e., 15mg patients thought they fell

asleep more easily. During the post-treatment week, the placebo patients thought they fell asleep more easily than the 15 mg group. The 15 mg group also had significantly greater ease in falling asleep than the 10 mg group at weeks 2, 5 and 6.The difference between the 10 mg and the placebo group was significant only during the post-treatment week, when 10 mg patients thought they fell asleep less easily.

2. Sleep Efficiency

Table 20 gives the mean and standard deviation of sleep efficiency by treatment group. There were no baseline differences between placebo, 10 mg and 15 mg and Sleep efficiency was significantly higher in the 15 mg group than in the placebo group at weeks 2 through 6 as well as at the end point. The 10 mg group had significantly greater sleep efficiency than placebo a weeks 2, 3, 4 and 5 but not at week 6 ($p = 0.070$) or end point ($p = 0.058$). There was no significant difference among the three treatment groups at week 7 (post-treatment). A secondary analysis evaluated **change in sleep efficiency from baseline.** The increase in efficiency was significantly greater with 15 mg than with placebo at all weeks except week 4 where a trend ($p = 0.065$) towards an increase with 15 mg compared to placebo was observed. The increase in efficiency was significantly greater with 15 mg than with 10 mg at weeks 2, 3 and 6 and at end point, with a trend toward the same result at weeks 4 and 5 ($p = 0.0706$ and $p = 0.0704$). Subjective total sleep time as assessed by Morning Questionnaire was numerically greater in both zolpidem groups than in placebo group. These differences were significant for 15 mg versus placebo at weeks 4, 5 and at end point and for 10 mg versus placebo. At the end point the 15 mg group was favored over the placebo group ($p = 0.053$).

3. Sleep Maintenance

The measures of PSG sleep maintenance were **wake time during sleep, wake time after sleep, and number of awakenings.**

Wake time during sleep was not significantly different among the treatment groups at any week of the double-blind treatment period, although it was always numerically lower in the 10 mg and 15 mg groups than in the placebo group. During the post-treatment week, the 15 mg group had significantly greater wake time during sleep time than the placebo or 10 mg group. There was no significant differences in **wake time after sleep.** There was no significant differences among the three groups with respect to the number of awakenings.

Measures of sleep maintenance from Morning Questionnaire were the **Subjective number of awakenings and the Subjective time awake after falling asleep.** At week 2, the 15 mg group reported significantly fewer awakenings than a the placebo or 10 mg groups. During the post-treatment week, there was a trend toward more awakenings with the 10 mg than with placebo. There were no significant differences among the treatment groups with respect to the reported time awake during sleep.

4. Sleep Stages

The percent sleep time in each of the four stages (1,2,3-4 and REM) was compared among the treatment groups. The only significant treatment differences were at weeks 3 and 4, when the 15 mg group had a lower percent of sleep time in REM sleep than the placebo group.

5. Sleep Quality

Patients evaluated sleep quality and the refreshing quality on a 4 point scale on the morning questionnaire (1 = excellent, 2 = good, 3 = fair, 4 = poor). During the double-blind treatment, sleep quality differed significantly among the groups at weeks 2 and 5. The 15 mg group had a significantly better quality of sleep than the 10 mg group at week 2 and the placebo group at week 5. At week 7 (post-treatment), both the zolpidem dose groups had poor sleep quality than placebo. The refreshing quality of sleep at week 2 was significant in the 15 mg group than in the 10 mg. At week 5, the 15 mg patients had significantly more refreshing sleep than either of the other two groups.

6. Psychomotor Performance Tests

The Digital Symbol Substitution Test (DSST) and Digital Symbol Copying Test (DSCT) were used to assess residual effects. There were no significant differences among the treatment groups at any week.

7. Morning Sleepiness

There was no difference among treatment groups in the patierts' rating of their ability to concentrate in the morning after medication was taken. There were significant treatment differences in morning sleepiness at week 4 and week 5. At week 4, the 10 mg group had significantly less morning sleepiness than the placebo and 15 mg groups. At week 5, the 10 mg group had a significantly lower morning sleepiness score than the placebo group.

8. Global Impression Therapy

The patient's impression of therapy was assessed at the first visit of week 7, after 5 weeks of double-blind treatment. A significantly greater proportions of patients in the 10 mg and 15 mg groups than in the placebo group though that treatment helped them fall asleep and that the medication was strong enough. In addition, a significantly greater proportion of the 15 mg than the placebo group said the medication helped them sleep longer and get a better night's sleep.

9. Tolerance to Zolpidem

In order to test for the development of tolerance to zolpidem, the change in efficacy variable from week 2 (the first week of active treatment) to week 6 (the last week of active treatment) was compared among treatment groups. Neither the polysomnographic nor the morning questionnaire data suggest the development of tolerance after five weeks of treatment with zolpidem. Among PSG parameters the only significant treatment difference was in the percent of time in stage 3-4 sleep. In this variable, test of change within each of the drug groups indicated there was a significant increase in stage 3-4 sleep in the placebo group ($p = 0.041$), but there was no significant change from baseline in the 10 mg ($p = 0.751$) or 15 mg ($p = 0.082$) groups. There were no significant treatment differences in the tolerance assessment of morning questionnaire or performance test data.

10. Post-Treatment Effects

The effect of discontinuing zolpidem was evaluated among the three treatment groups by (a) comparing the mean results from each night of post-treatment period and (b) comparing the mean changes from baseline (mean values from each post treatment day minus week 1 values). Table 21 displays the results of the among-treatment comparisons at post-treatment Day 1 for latency persistent sleep, sleep efficiency, wake time during and after sleep ard sleep quality.

Although there was no significant difference between the 10 mg and placebo groups in raw mean latency to persistent sleep score on the first post treatment night, the 10 mg group ($p = 0.033$) did show a significantly greater increase from baseline than the placebo group. There was also a trend toward poorer sleep quality with 10 mg ($p < 0.10$), but not difference in sleep efficiency or wake time during sleep.

The 15 mg group did not differ significantly from the placebo group on sleep latency. There was a significantly greater wake time during sleep with 15 mg, but this sleep loss did not result in significant differences in sleep efficiency. The 15 mg mean sleep quality on the first post-treatment night was significantly worse than that seen with placebo, but there were not differences in the change from baseline between the two treatment groups. These primary comparisons did not indicate objective evidence of post-treatment deterioration in sleep, although there was an indication of poorer sleep quality with zolpidem than with placebo during the first night of post-treatment week.

11. Evaluable Data Set Analysis

As the difference between the Intent-to-treat data set and evaluable data set was very little, the sponsor performed an evaluable data set analysis only on latency to persistent sleep and sleep efficiency. There were no differences from the analyses on the Intent-to -treat data set.

Safety

TEAE (Treatment Emergent Adverse Events) occurred approximately equal proportion of patients, in the three treatment groups. Dose related drowsiness, dizziness, nausea and dyspepsia occurred in a greater proportion of zolpidem patients than placebo patients.

Reviewer's Evaluation and Conclusions

The sponsor's statistical analysis indicates that both the 10mg and 15 mg doses seem to have had an early beneficial effect (within the first week of treatment) on **latency to persistent sleep, sleep efficiency and total sleep time** that was maintained throughout the 30 days of treatment evaluation. There was no evidence of residual effect with zolpidem. The sponsor states that Stage 3-4 was preserved, although there were minor decrease in REM at weeks 3 and 4 with the 15 mg dose. There was no evidence of tolerance and no significant treatment difference in latency or efficiency on the first day off active treatment. Both doses of zolpidem were judged by patients to have helped them fall asleep, and the 15 mg dose was judged to have helped them sleep longer and get a better night's sleep. Overall, treatment-emergent adverse event incidence rates in the zolpidem groups were similar to that in the placebo group. There were no clinically significant abnormalities in laboratory tests of vital signs. The reviewer's independent statistical analyses on the primary and secondary efficacy variables agree with the sponsor's analyses.

IV LSH **Zolpidem in outpatients with Insomnia**

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with **insomnia.** Each patient was randomly assigned to one of three treatment groups. Assignment to zolpidem 10mg, 15 mg, and placebo was done in a 4:4:5 ratio in order to ensure that approximately equal numbers of patients would complete double-blind therapy in each treatment group (in the event of a high placebo withdrawal rate).

The following table illustrates the study design and schedule of treatment administration following randomization.

Table
Study Design
LSH

	Day of Week						
Week	1	2	3	4	5	6	7
1	P	P	P	T	T	T	T
2	T	T	T	T	T	T	T
3	T	T	T	T	T	T	T
4	T	T	T	T	T	T	T
5	T	T	T	T	T	T	P
6	P	P	P				

P = placebo
T = randomized treatment (zolpidem or placebo)

Study Population

Outpatient insomniacs, aged 18 to 60, were screened to rule out any significant medical or psychiatric disorder. In addition, patients were required to have insomnia for at least three months preceding screening. 145 (81 Female/64 Male) patients were randomized and 118 completed all six weeks of the experimental phase. Fifty-four were randomized to placebo 45 to zolpidem 10 mg, and 46 to zolpidem 15 mg. Twenty-three of 145 (15.9%) discontinued during the double-blind portion of the study. The data from two centers (Docherty and Kann) were combined to provide relatively equal numbers of patients for statistical analysis. The Outcome Measures were Morning Questionnaire, clinical global Impression, sleep Log and adverse Event Reports. The primary Efficacy Variables were Subjective Sleep Latency and Subjective Total Sleep Time from Morning Questionnaire; the Secondary Efficacy Variables were Subjective Number of awakenings, Sleep Quality, Morning Sleepiness and Patients Global Impression of the Therapy.

Study Procedures

At each visit, patients were dispensed study drug in a blister card for the next study week. Patients were instructed to take the study medication 30 minutes before their usual time of falling asleep and to get into bed as soon as possible after taking their medication.

Patients were instructed to try to keep their bedtime and arising time the same throughout the study. Patients completed a Morning Questionnaire on Days 1, 2, 3, and 7 (after the first three and the last treatment night) of each week. Patients completed an additional questionnaire addressing their overall impression of the study drug on the day they reported to the site to begin week 5.

Efficacy Analysis by the Sponsor

The sponsor did an analysis on the Intent-to-Treat population by carrying forward the last observation (LOCF), which incorporated all available data from any randomized patient. In addition, he did an evaluable patient analysis to confirm the results of the Intent-to-Treat analysis. The sponsor has performed all efficacy analyses by grouping together the data from the Docherty and Kann study centers to provide relatively equal numbers of cases from all sites. The equality of the distribution of **baseline** factors was analyzed using the (controlling for center) for **Categorical Variables** and **ANOVA** for **Continuous Variables.** In addition, the average was calculated for ordered categorical variables and analyzed by **ANOVA.**

Treatment effects on **Subjective Sleep Latency** were tested by Descriptive statistics (means and standard errors) were calculated by the product-Limit Estimator Both of these methods are non-parametric methods commonly used to analyze the time to an event, such as survival, where some observations are "censored". Censored data commonly arise when, for some patients, an event might not be observed because the observation period is terminated. For those patients, the time to the event is known only to be longer than the length of the observation period. In the analysis of subjective sleep latency, these methods were required because **eleven** latencies from **eight** patients were "censored". That is, they were known only to be greater than the time spent in bed (the observation period) because the patients reported that they had not fallen asleep. The value used when a patient reported not having fallen asleep was the number of minutes between turning lights out and the time of arising. If the time of arising was not reported, then the cut-off point was either 480 minutes or the time between lights out and the time of completion of the data form, whichever was less.

For each patient, the estimation procedure calculated the proportion of patients with a longer subjective sleep latency. Because no assumption was made about the distribution of the time to the event (e.g., Subjective Latency) the procedure is considered to be non-parametric.

To provide a test for the effect of treatment on subjective sleep latency that controlled for the effect of investigator, a proportional hazards stratified by investigator was adopted. Tests for statistical significance of the treatment effect were evaluated by the and compared with the distribution. If the overall test of the drug effect was statistically significant at the 0.05 level, then separate tests (using the statistic as before) for each treatment were performed and reported. A key assumption of the proportional hazards model is that the hazard of the event at any time within each treatment group is proportional to some baseline hazard. Use of the investigator-stratified model accommodated potentially non-proportional hazards among

investigators. The parameters included in the proportional hazards model provided separate estimates of treatment effects, relative to placebo, for the 10 mg zolpidem group and 15 mg zolpidem group. Thus a binary covariate was defined to have a value of 1 if the observation arose from the 10 mg group, zero otherwise; a similar binary covariate was defined for observation arising form the 15 mg group. The sponsor analyzed the **Tolerance** and **Post-treatment effects** for the primary efficacy variables by using **ANOVA.**

The estimate of tolerance for each patient was computed as the difference between the mean response during week 2 and the mean response during week 5. Post-treatment effects were estimated using two methods: **1)** by comparisons of values at each post-treatment day (among treatment groups) and **2)** by comparisons of within-patient changes from baseline at each post-treatment day (among the within-treatment groups).

Two additional steps were used in the analysis of tolerance and post-treatment effects for subjective sleep latency. 1) Censored observations were treated as though they were uncensored and were included in the analysis; 2) The use of the logarithm applied to the mean sleep latency has been found in this and other zolpidem study reports to both normalize the data and reduce heteroscedasticity. In analyses of tolerance and post-treatment effects, ANOVA treatment effects were noted if the overall p-value was < 0.05. If this level was reached, pair-wise comparisons were performed. P-values that were between 0.05 and 0.10 were noted as trends. **Table 22** gives the summary characteristics of the 145 randomized patients. At **baseline**, the three treatment groups zolpidem 10 mg, zolpidem 15 mg and placebo did not differ significantly for any **demographic characteristic.** No significant differences were found among the treatment groups for usual sleep latency or usual sleep time **(Table 23).** There was a significant treatment-by-center interaction **(p = 0.0059)** for usual sleep ime. Separate analyses by sponsor indicated that for Cohn's center, the 15 mg had a significantly larger mean (mean = 2.875, p = 0.0305) than the placebo group (mean = 2.33). Data from two of the other centers exhibited the same (though nonsignificant) pattern. **Table 24** gives the summary of **Primary Efficacy Results** for **Subjective sleep Latency, Subjective Total Sleep Time, Subjective Number of Awakenings, and Sleep Quality for baseline, Week 2, Week 3, Week 4, Week 5, Post-Treatment and PostTreatment Day 1.**

<u>Subjective Sleep Latency:</u> Mean Subjective Sleep Latency was numerically shorter in both zolpidem groups than in the placebo group at all treatment weeks. There were significant differences among the three treatment groups at weeks 2, 3, 4 and 5 **(Table 24).** The 10 mg group had significantly shorter sleep latency than placebo at all treatment weeks, while mean sleep latency in the 15 mg groups was significantly shorter than that in the placebo mean at weeks 2, 3, and 4. **Figure 1** illustrates the differences in the distribution of subjective sleep latencies among the three treatment groups during the first week of treatment (week 2), based on **Product-Limit**

estimates. The curves for 10 mg and 15 mg groups are similar. After approximately 20 minutes, these curves separate from placebo group; i.e., the zolpidem groups have proportionately fewer patients whose latency times were ≥ 20 minutes than did the placebo group. In fact, approximately 30% of the placebo patients had sleep latencies > 60 minutes, compared to 10% of the patients in each of the zolpidem groups. **Figure 2** contains graphs of the distribution of subjective sleep latencies for weeks 2-6 and graphs of the Product-Limit Estimates by Study Center at each period. These displays illustrate the **non-proportionality** of the estimated curves for each center, supporting the use of the **stratified proportional hazards model.** At **baseline,** mean subjective sleep latency was numerically higher in both zolpidem groups than in the placebo group. **Table 25** contains an analysis that the sponsor performed to calculate the differences in mean responses between the baseline placebo period and each treatment week (i.e., differences in the logarithm of each patient's average latency for two weeks). This analysis showed that the decrease in sleep latency from baseline was significantly greater for both zolpidem groups than for placebo at weeks 2, 3 and 4, and for the 10 mg group at week 5.

Subjective Total Sleep Time: At week 2, subjective total sleep times were significantly longer in both zolpidem groups than in the placebo group **(Table 24).** Compared with the placebo group, there was a trend toward increased subjective total sleep time in the 15 mg group at week 3. Even with the increases in sleep times in the placebo group at the later weeks of the study, mean total sleep times in the zolpidem groups were consistently numerically greater than in the placebo group. The sponsor did a supplemental analysis on the arithmetic differences in mean subjective total sleep time between the baseline placebo period each treatment week. Changes from baseline were significantly greater for both zolpidem groups than the placebo group at week 2.

Subjective Number of Awakenings: Overall treatment differences were significant at weeks 2 and 3. During week 2, the 10 and 15 mg groups each had significantly smaller mean number of awakenings than placebo group **(Table 24).** During week 3, the mean number of times awakened in the placebo group **(1.9)** differed significantly from the mean in the 15 mg group **(1.2).** However, mean number of awakenings in the 10 mg group **(1.4)** did not differ significantly from either placebo or 15 mg.

Sleep Quality: Patients evaluated sleep quality on a four-point scale (1 = excellent, 2 = good, 3 fair, and 4 poor). Significant treatment differences were observed at weeks 2 and 3. Compared with the placebo group, sleep quality was significantly better in the 10 mg grout at week 2 and in the 15 mg group at weeks 2 and 3. There were trends toward significant differences at week 4 (when both zolpidem groups had better sleep quality than the placebo group) and during the post-treatment week (when the 15 mg group showed a trend toward poorer sleep).

Morning Sleepiness: Patients recorded their degree of morning sleepiness by drawing a ling on a visual analog scale, where 0 mm = very sleepy and 100 mm = not at all sleepy. There were no significant differences among the three treatments during the treatment period, although a trend was seen at week 5 in the 15 mg group (more sleepiness for this group than for the 10 mg and placebo groups). The 15 mg group also reported significantly more morning sleepiness than placebo at week 6 (post treatment).

Global Impression of Therapy: The Global Impression of Therapy was collected only once (at the completion of **4th week of treatment**). patient's impressions of therapy in both the 10 mg and 15 mg groups were significantly better than placebo on every rating. Zolpidem patients felt that the therapy had helped them to fall asleep, fall asleep faster, sleep longer and get a better night's sleep, and that the medication was strong enough.

End Point Analysis: Analyses at the endpoint (carrying forward last observation for each patient) demonstrated a significant treatment difference for subjective sleep latency with both zolpidem groups showing a significantly shorter sleep latency than placebo. There were **trends** toward significant differences in total sleep time for the 10 and 15 mg treatment groups versus placebo ($p=0.0501 < 0.1$) and in the number of awakenings for 15 mg versus placebo ($p=0.0735 < 0.1$).

Analysis of Tolerance to Treatment Effects: The sponsor performed an analysis of treatment tolerance comparing changes in subjective sleep latency and subjective total sleep time after one week to changes after four weeks of treatment (week 2 minus Week 5) showed no loss of treatment effect in any of the three groups **(Table 26).**

Analysis of Post-Treatment Effects: Sleep variables were evaluated daily following abrupt discontinuation of zolpidem (switching patients to placebo in a single-blind fashion) during the post-treatment week, by comparing subjective sleep latency, subjective total sleep time, morning sleepiness, number of awakenings and sleep quality (including changes from baseline for the first three variables) at Days 1, 2, 3, and 4 of the placebo phase after the last dose of double-blind treatment. There were no significant differences among the three treatments in mean sleep latency at any day or for the week overall. **Table 27** presents day-by-day differences in subjective sleep latency from baseline (i.e., between the baseline placebo period and post treatment period) within each treatment group. There were no significant differences among the three treatment groups for the individual days or for the post-treatment week overall. Sleep latency was generally shorter during the study than during baseline. The only exception was a 30-minute increase in the 15 mg group on the first night **off zolpidem.** This increase did not, however, reach statistical significance. **Table 28** gives the Daily Mean Subjective Total Sleep Time (minutes) during Post-Treatment Week. Subjective total sleep time generally improved, except at Night 1, when the 15 mg group showed a trend toward shorter sleep time than

the placebo group. Table 29 gives the mean change in Subjective Total Sleep Time from **baseline** within each treatment and the results were compared among the groups. In the 15 mg group, total sleep time was 30 minutes less on the first post-treatment night than at baseline. This decrease was significantly different from the increases in the placebo (23 minutes) and 10 mg (14.1 minutes) groups. Total sleep time was not different from baseline on the next two nights, and was greater than baseline on the **fourth** post-treatment night. For the overall post-treatment week, the mean increase from baseline in subjective total sleep time for the 15 mg group was significantly smaller than that for placebo. Within-treatment comparisons with baseline revealed a significant decrease in subjective total sleep time in the 15 mg group on the first posttreatment day. The following significant increases from baseline were seen during the post-treatment week; in the placebo group on days 2, 3, and 4; in the 10 mg group on Days 2 and 3 and in the 15 mg group on Day 4. Throughout the post-treatment week, subjective total sleep time was numerically greater than baseline except on Day 1 in the 15mg group. **Table 30** gives the mean number of awakenings and Sleep quality and Mean change from Baseline During the First Day of the Post-Treatment Week. No overall treatment differences were observed. The within-treatment analysis indicated significant decreases **from baseline** in subjective number of awakenings for the placebo and 10 mg groups. **Table 31** presents the means values of morning sleepiness for each day of the posttreatment week. The sponsor performed a by-center analysis due to treatment-by-center interactions at Days 2 and 3. On Day 2, there was a significant increase in morning sleepiness with 15 mg compared to placebo at the Leppik center. Sleepiness with 15 mg was decreased compared to placebo at the other centers. On Day 3, there was a trend toward increased morning sleepiness with 15 mg compared to placebo at the Leppik center. **Table 32** gives the changes in daily values from the baseline placebo period to the post-treatment period. The 15 mg group showed a trend toward greater morning sleepiness than placebo on Day 1. But there was no significant change from baseline within the 15 mg group. In general, there may have been a small post-treatment effect (not evident in all measures or all analyses) in the 15 mg group at Day 1 post-treatment.

Reviewer's Evaluation and Conclusions:

The sponsor's analysis indicates that the 10 mg dose had an early beneficial effect (within the first week of treatment) on Subjective sleep latency and Total sleep time that was maintained throughout the four weeks of treatment evaluation. The sponsor states that there was no disturbance of sleep on the nights after discontinuation of 10 mg zolpidem. Similar beneficial hypnotic effects were seen with 15 mg. There was evidence of decreased total sleep time on the first night after 31 days of treatment (Post-treatment day 1) with 15 mg. Both doses of zolpidem were judged by patients to have helped them fall asleep, fall asleep faster, sleep longer and sleep better.

The reviewer did an independent non-parametric analysis on the Primary efficacy variables.(subjective sleep latency and subjective total sleep time and on the Secondary efficacy variables (number of awakenings, sleep quality and morning sleepiness). **Table 33 (Reviewer's)** gives the summary of primary and secondary efficacy results by reviewer. With respect to the Subjective sleep latency, there were significant differences among the three treatment groups all 4 treatment weeks. **(Table 33).** The 10 mg group had significantly shorter sleep latency than placebo at all 4 treatment weeks, while the mean sleep latency in the 15 mg group was significantly shorter than that of the placebo mean at weeks 2, 3 and 4. At week 2, Subjective total sleep times were significantly longer in 10 mg and 15 mg groups than in the placebo group and at week 3, the Subjective total sleep time was significantly longer in the 15 mg group as compared to placebo- **(Table 33).** During week 2, the 10 mg and 15 mg groups each had significantly smaller mean number of awakenings than placebo **(Table 33).** During week 3, the mean number of times awakened in the placebo group differed significantly from the mean in the 15 mg group. Compared with placebo, sleep quality was significantly better in the 10 mg group at week 2, and in the 15 mg group at weeks 2 and 3 and a trend toward poorer sleep was observed during the post-treatment week **(Table 33).** With respect to morning sleepiness, there were no significant differences among the three treatment groups at weeks 2, 3 and 4, but more sleepiness in the 15 mg group than in 10 mg and placebo groups at week 5. The reviewer performed a non-parametric analysis of treatment tolerance by comparing the changes in subjective sleep latency and subjective total sleep time after one week to changes after four weeks of treatment (week 5 minus week 2) and found no loss of treatment effect in any of the three groups. With respect to subjective sleep latency ($p=0.0751$); but there was a trend towards loss of treatment effect in the three treatment groups. With respect to subjective total sleep time ($p=0.042$). The reviewer also checked the sponsor's analysis of Global Impression of Therapy and found that the patients' impressions of therapy in both the 10 mg and 15 mg groups were significantly better than placebo on every rating. Both the doses of zolpidem were judged by patients to have helped them fall asleep, fall asleep faster, sleep long and sleep better. In general, the reviewer's independent alternate statistical analyses are in agreement with the sponsor's analyses.

V. Overall conclusions (which may be conveyed to the sponsor)

This submission contains statistical evidence strongly supportive of the efficacy of **zolpidem** as an **hypnotic agent** in adults in sleep laboratories and as outpatients, both for **Insomnia.** Doses **7.5** and **10 mg** of **zolpidem** appear to provide significantly better response for most efficacy variables than does placebo, in the case of **Insomnia** and doses **10** and **15 mg** of **zolpidem**, in the case of **Insomnia.** However, in the **Study** 145 patients were randomized to form the Intent-to-

treat data set and 23 (15.9%) patients discontinued during the double-blind portion of the study; thus 118 patients completed the study. In order to explore the effect of dropouts, the sponsor should submit the observed cases analyses on the intent-to-treat population.

R.Srinivasan, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius SEM 10/2/90

Dr. Dubey 10-25-90

cc:
Orig. NDA 19-908
HFD-120
HFD-120/Dr.Leber
HFD-120/Dr.Laughren
HFD-120/Dr.Collins
HFD-120/CSO
HFD-344/Dr.Lisook
HFD-713/Dr.Dubey [File: DRU 1.3.2]
HFD-713/Group 2 file
HFD-713/Dr.Srinivasan
Chron.

This review contains 24 pages followed by 33 Tables and 13 pages of Figures 1 and 2.

TABLE 1

STUDY LSH

LATENCY TO PERSISTENT SLEEP (MINS.)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	27.1	23.8+	17.0*	17.4*	18.7	20.6+	0.003
SD	26.6	21.3	14.5	16.7	18.1	26.0	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT. COMPARISON (ALL SIX GROUPS).

TABLE 2

STUDY LSH

SLEEP EFFICIENCY (%)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	87.8	89.1+	91.7*	91.8*	91.0+	91.1+	<0.001
SD	8.6	7.1	6.8	6.9	7.4	08.8	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 2a

STUDY LSH

TOTAL SLEEP TIME (MINS.)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	421.6	427.7+	440.3*	440.6*	436.9+	437.1+	0.0009
SD	41.1	34.1	32.4	33.0	35.3	42.3	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 3

STUDY LSH

WAKE TIME DURING SLEEP (MINS.)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	31.4	26.5+	21.2*	21.4*	21.3+	21+	0.027
SD	30.9	22.3	24.7	24.0	21.9	25.0	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 4

STUDY LSH

NUMBER OF AWAKENINGS

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	6.7	5.8+	5.0*	5.3*	5.5+	4.7+	0.0244
SD	4.2	4.0	3.6	4.0	5.1	4.0	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 5

STUDY L5H

SLEEP STAGES %

STAGE		PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
1								
	MEAN	9.6	9.5+	9.4	8.8	8.2+	8.7+	0.515
	SD	5.7	6.1	6.7	5.7	4.4	5.6	
2								
	MEAN	56.7	58.6+	56.2	58.7	59.3+	58.5+	0.120
	SD	7.3	8.0	8.3	8.8	11.0	8.9	
3 - 4								
	MEAN	12.4	13.5+	15.7*	13.6	14.5+	16.4+	0.040
	SD	8.1	8.5	8.5	8.4	8.7	9.9	
REM								
	MEAN	20.9	18.1+	18.4*	18.5*	17.5+	15.9+	<0.001
	SD	5.7	4.6	4.3	5.5	6.5	5.2	
	N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05).
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT. COMPARISON (ALL SIX GROUPS).

TABLE 6a

STUDY LSH

ABSOLUTE REM SLEEP (MINS.)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	88.7	77.9+	81.0*	81.5+	76.9+	70.5+	<0.001
SD	26.9	22.1	20.3	25.0	30.5	24.5	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 6b

STUDY LSH(

LATENCY TO REM SLEEP (MINS.)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	83.4	95.0+	103.8*	107.7*	121.0+	130.3+	<0.001
SD	36.4	35.2	43.1	48.2	52.5	51.8	
N	101	52	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 7

STUDY LSHS

SUBJECTIVE SLEEP LATENCY (MINS)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	28.8	20.2+	18.9*	18.2*	18.1+	13.6+	<0.001
SD	30.8	13.9	12.2	15.4	18.8	9.7	
N	102	51	102	102	50	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 8

STUDY LSH

EASE OF FALLING ASLEEP@

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	46.4	31.4+	30.1	31.0	27.2+	20.1+	<0.001
SD	25.9	21.4	23.9	27.5	26.4	21.6	
N	102	51	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).
@ :0=VERY EASY, 100=NOT AT ALL EASY.

TABLE 9

STUDY LSH

SUBJECTIVE TOTAL SLEEP TIME (HOUR)

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	7.1	7.4+	7.3	7.2	7.3+	7.6+	0.263
SD	1.1	0.7	1.2	1.4	1.0	0.5	
N	102	51	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).

TABLE 10(a)
STUDY LSH

SLEEP QUALITY@

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	2.7	2.4+	2.2*	2.2*	2.3+	2.1+	<.0001
SD	0.8	0.7	0.8	0.8	0.8	0.7	
N	102	51	102	103	51	51	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).
@: 1=EXCELLENT, 2=VERY GOOD, 3=FAIR, 4=POOR.

TABLE 10(b)
STUDY LSH

REFRESHING QUALITY OF SLEEP @

DOSE	PLC	5MG	7.5MG	10MG	15MG	20MG	P-VALUE (x)
MEAN	2.3	2.2+	2.1	2.1	2.1+	2.1+	0.083
SD	0.7	0.8	0.8	0.7	0.7	0.7	
N	102	52	102	103	51	50	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO (P<.05)
+: INCLUDED FOR DOSE-RESPONSE INFORMATION ONLY. NOT TESTED AGAINST PLACEBO.
(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).
@: 1=EXCELLENT, 2=VERY GOOD, 3=FAIR, 4=POOR.

TABLE 11
LSH
MULTIPLE COMPARISONS OF SLEEP PARAMETERS+

	PLC N=102	5MG N=52	7.5MG N=102	10MG N=104	15MG N=51	20MG N=51	P-VALUE (x)
LATENCY TO PERSISTENT SLEEP (MINS)	27.1 A	23.8 A,B	17.0 B	17.4 B	18.7 B	20.6 A,B	0.004
EFFICIENCY(%)	87.8 A	89.1 A,B	91.7 B	91.8 B	91.0 A,B	91.1 A,B	0.001
TOTAL SLEEP TIME (MINS.)	421.6	427.8	440.3	440.3	436.9	437.1	0.0009
AWAKENINGS(#)	6.7 A	5.8 A,B	5.0 B	5.3 A,B	5.5 A,B	4.7 B	0.024
SUBJECTIVE LATENCY (MINS.)	28.8 A	20.2 A	18.9 A	18.2 B	18.1 B	13.6 B	0.001
STAGE REM(%)	20.9 A	18.1 B,C	18.4 B,C	18.5 B	17.5 B,C	15.9 C	0.0001

(x): OVERALL TREATMENT COMPARISON (ALL SIX GROUPS).
+: TWO TREATMENTS DIFFER SIGNIFICANTLY IF AND ONLY IF THERE ARE NO LETTERS IN COMMON BETWEEN BOTH.

Table 12

LSH

Descriptive statistics for combined placebo periods

	*Night 1 (n = 86)	*Night 2 (n = 29)
Efficiency (%)	94.9(3.4)	85.3(13.2)
Latency (Mins.)	8.7(9.1)	17.9(26.8)

* Night I : Usual bed time
* Night II : 3 Hour phase advance

Table 13

LSH

Latency to persistent sleep (Mins.)

	Crossover I		Crossover II		p-value
	Mean	Standard Deviation	Mean	Standard Deviation	
Placebo	24.5	37.7	12.6	11.6	0.602
5 mg	-	-	9.6	10.2	(t-test)
10 mg	17.2	21.8	-	-	
15 mg	-	-	5.9	4.3	
20 mg	25.6	44.1	-	-	
(x) = p-value	0.834		0.152		

(x): overall treatment comparison

Table 14

Sleep Efficiencies (Night 2)
(Efficiency(%)

	Crossover I	Crossover II
Placebo	84.5(13.0)	85.9(13.7)
5 mg	-	93.4(5.0)
10 mg	92.8(6.1)	-
15 mg	-	93.7(5.4)
20 mg	89.2(14.2)	-
(x): p-value	0.129	0.034

(x): overall treatment comparison

Table 15

LSH

Subjective Sleep Duration (Mins.)
Mean (Standard Deviation)

	Crossover I	Crossover II
Placebo	415.2(57.4)	432.3(44.1)
5 mg	-	447.6(37.1)
10 mg	456.1(45.1)	-
15 mg	-	464.1(16.8)
20 mg	442.6(39.2)	-
(x): p-value	0.013	0.012

(x): overall treatment comparison

Table 16

LSH

Primary Efficacy Variables

		Crossover I	Crossover II
Mean (S.D) wake time during sleep	Placebo	53.7(64.4)	46.2(58.9)
	5 mg	-	23.7(21.8)
	10 mg	19.9(25.3)	-
	15 mg	-	19.3(14.6)
	20 mg	19.3(31.9)	
(x) = p-value		0.024	0.107
Mean (S.D) Number of awakenings	Placebo	3.9(2.2)	5.9(3.5)
	5 mg	-	5.4(3.4)
	10 mg	5.5(2.8)	-
	15 mg	-	5.3(2.9)
	20 mg	4.8(4.5)	-
(x) = p-value		0.431	0.712
Mean (S.D) of Mins. awake after falling asleep (Subjective) .	Placebo	49.4(51.9)	32.8(28.8)
	5 mg	-	25.8(30.5)
	10 mg	20.8(24.4)*	-
	15 mg	-	13.4(12.9)*
	20 mg	17.0(33.5)*	-
(x) = p-value		0.021	0.043
Mean (S.D) quality of sleep	Placebo	2.7(0.8)	2.6(0.8)
	5 mg	-	2.1(0.7)*
	10 mg	2.3(0.6)*	-
	15 mg	-	2.1(0.4)*
	20 mg	2.4(0.7)	-
(x) = p-value		0.151	0.333

*: significantly different from placebo ($p<0.05$)
(x): overall treatment comparison

TABLE 17
LATENCY TO PERSISTENT SLEEP (MIN.)
LSH

WEEK		PLACEBO (N=24)	10MG (N=25)	15MG (N=25)	P VALUE@
BASELINE	MEAN	49.9	35.8	47.0	0.250
	SD	33.4	24.5	31.5	
2	MEAN	44.7	22.9*	21.6*	0.003
	SD	29.1	14.0	23.5	
3	MEAN	51.1	24.4*	26.5*	0.023
	SD	50.0	14.5	24.3	
4	MEAN	56.2	20.3*	21.6*	0.001
	SD	47.0	12.6	11.7	
5	MEAN	43.8	23.5*	23.3*	0.033
	SD	37.4	16.9	33.9	
6	MEAN	48.0	25.8	28.1*	0.029
	SD	38.5	13.7	25.6	
END POINT	MEAN	46.6	25.9	25.6*+	0.004
	SD	38.4	13.8	25.0	
POST TREAT.	MEAN	42.9	47.1	47.7	0.692
	SD	35.0	30.2	32.6	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO. $p<0.05$
+: SIGNIFICANTLY DIFFERENT FROM 10MG, $p<0.05$
@: ANALYSIS PERFORMED ON THE LOGARITHM OF LATENCY

TABLE 18
CHANGE IN LATENCY TO PERSISTENT SLEEP (MIN.) FROM BASELINE
(WEEK 1)
LSH

WEEK		PLACEBO	10MG	15MG	P VALUE (x)
2	MEAN	-5.2	-12.9	-25.4*+	0.004
	SD	32.9	23.9	38.0	
	N	24	26	25	
3	MEAN	1.3	-3.1	-20.4*	0.038
	SD	35.8	15.9	42.5	
	N	24	24	24	
4	MEAN	4.7	-12.8	-26.9*	0.047
	SD	45.2	22.4	32.6	
	N	23	22	22	
5	MEAN	-7.7	-9.6	-19.1	0.140
	SD	37.3	22.1	51.5	
	N	23	22	22	
6	MEAN	-3.4	-7.3	-20.3*+	0.016@
	SD	36.0	19.0	36.0	
	N	23	22	22	
END POINT	MEAN	-3.3	-9.9	-21.5*+	0.001
	SD	35.2	24.9	34.3	
	N	24	26	25	
POST TREAT.	MEAN	-8.5	14.0*	-0.7	0.050
	SD	35.2	32.0	36.9	
	N	23	22	22	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO. $p<0.05$
+: SIGNIFICANTLY DIFFERENT FROM 10MG, $p<0.05$
@: SIGNIFICANT TREATMENT-BY-INVESTIGATOR INTERACTION, $p<0.05$
(x): OVERALL COMPARISON OF ALL TREATMENT GROUPS.

TABLE 19
SUBJECTIVE SLEEP LATENCY (MIN.)
LSH

WEEK		PLACEBO	10MG	15MG	P VALUE (a)
BASELINE	MEAN	70.4	57.0	61.0	0.955
	SD	50.4	28.6	33.0	
	N	24	25	25	
2	MEAN	61.1	43.5	33.5*	0.032
	SD	39.5	32.6	32.8	
	N	24	26	25	
3	MEAN	63.2	34.9@	30.7*	0.014
	SD	50.0	18.3	26.3	
	N	24	24	24	
4	MEAN	72.7	37.6*	32.3*	0.001
	SD	52.6	22.4	26.7	
	N	23	22	22	
5	MEAN	69.2	37.5*	35.2*	0.003
	SD	55.2	19.0	35.4	
	N	23	22	22	
6	MEAN	56.6	38.4@	31.7*	0.004b
	SD	39.5	22.0	22.9	
	N	29	22	22	
END POINT	MEAN	56.1	38.3@	30.0*	0.002b
	SD	38.7	21.6	22.2	
	N	24	26	25	
POST TREAT.	MEAN	47.5	62.3	78.2	0.129
	SD	30.8	48.3	66.1	
	N	23	22	22	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO. $p<0.05$
@: DIFFERENT FROM PLACEBO, $p<0.10$
(a): ANALYSIS PERFORMED IN LOG OF LATENCY
b: SIGNIFICANT TREATMENT-BY-CENTER INTERACTIONS, $p<0.05$

TABLE 20
SLEEP EFFICIENTY (%)
LSH

WEEK		PLACEBO	10MG	15MG	P VALUE (a)
BASELINE	MEAN	80.8	85.3	80.6+	0.047
	SD	8.9	7.7	8.9	
	N	24	26	25	
2	MEAN	81.6	88.1*	88.1*	0.022
	SD	9.8	6.3	8.0	
	N	24	26	25	
3	MEAN	80.3	87.9*	88.0*	0.004
	SD	12.4	6.9	8.3	
	N	24	24	24	
4	MEAN	81.8	88.1*	89.1*	0.028
	SD	13.0	9.2	6.2	
	N	23	22	22	
5	MEAN	83.2	89.3*	88.0*	0.007
	SD	9.7	6.7	8.8	
	N	23	22	22	
6	MEAN	80.7	87.9@	87.3*	0.027
	SD	13.4	6.4	8.7	
	N	23	22	22	
END POINT	MEAN	80.8	87.6@	87.6*	0.019
	SD	12.1	6.5	8.3	
	N	24	26	25	
POST TREAT.	MEAN	81.9	83.1	79.9	0.875
	SD	13.2	10.2	11.8	
	N	23	22	22	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO. $p<0.05$
@: DIFFERENT FROM PLACEBO, $p<0.10$
+: SIGNIFICANTLY DIFFERENT FROM 10MG, $p<0.05$
(a): ANALYSIS PERFORMED ON THE LOGIT OF EFFICENCY.

TABLE 21
MEAN RESULTS FOR FIRST POST-TREATMENT DAY
AND MEAN CHANGE FROM BASELINE
(WEEK 7 VALUES MINUS WEEK 1 VALUES)
LSH

VARIABLE		PLACEBO (N=23)	10MG (N=22)	15MG (N=22)	P-VALUE
LATENCY TO PERSISTENT SLEEP (MIN.)	MEAN	48.2	63.9	60.1	0.211
	SD	54.8	55.6	56.6	
	MEAN CHNG.	-3.3	30.8*	11.7#	0.013
	SD	48.7	55.0	58.6	
SLEEP EFF. (%)	MEAN	78.4	77.9	76.0	0.836
	SD	20.3	17.6	15.9	
	MEAN CHNG.	-2.2	-8.6	-5.1	0.112
	SD	17.0	14.8	13.8	
WAKE TIME AFTER SLEEP (MIN.)	MEAN	32.2	8.8	4.9	0.384
	SD	89.4	27.3	17.1	
	MEAN CHNG.	24.6	5.4	-1.8	0.494
	SD	92.3	28.3	23.3	
WAKE TIME DURING SLEEP (MIN.)	MEAN	25.3	38.1	53.8*#	0.027a
	SD	17.9	43.5	54.2	
	MEAN CHNG.	-12.6	7.1	15.1@	0.074
	SD	39.7	29.9	57.1	
SLEEP QLTY. (b)	MEAN	2.8	3.2@	3.4*	0.028
	SD	0.8	0.8	0.8	
	MEAN CHNG.	0.1	0.4	0.4	0.416
	SD	1.1	0.9	0.9	

*: SIGNIFINCANTLY DIFFERENT FROM PLACEBO, p<0.05
@: DIFFERENT FROM PLACEBO, p<0.10
#: DIFFERENT FROM 10MG, p<0.10
a: SIGNIFICANT TREATMENT BY CENTER INTERACTION, p<0.05
(b): SCALE: 1=EXCELLENT, 2=GOOD, 3=FIAR, 4=POOR

TABLE 22
LSH
DEMOGRAPHY AT RANDOMIZATION

VARIABLE	PLACEBO N=54	10MG N=45	15MG N=46	OVERALL N=145	P VALUE (a)
AGE (YEAR)					
MEAN (SD)	43.6(12.2)	47.2(12.1)	44.2(11.1)	44.9(11.6)	0.217
AGE (YEAR)					
<50	35(65%)	25(56%)	31(67%)	91(63%)	0.477 b
>50	19(35%)	20(44%)	15(33%)	54(37%)	
RACE					
CAUCASIAN	49(91%)	43(96%)	42(91%)	134(92%)	0.391 b
BLACK	4(7%)	2(4%)	2(4%)	8(6%)	
HISPANIC	1(2%)	0	0	1(<1%)	
ASIAN	0	0	2	2	
GENDER					
MALE	22(41%)	22(49%)	20(43%)	64(44%)	0.730 b
FEMALE	32(59%)	23(51%)	26(57%)	81(58%)	
HEIGHT(CM)					
MEAN (SD)	169.9(9.7)	170.8(9.6)	171.2(9.6)	170.6(9.4)	0.811
WEIGHT (KG)					
MEAN (SD)	74.5(16.8)	75.8(17.2)	73.1(17.3)	74.5(16.7)	0.697

(a): SIGNFICANCE LEVEL OF OVERALL TREATMENT EFFECT (ANOVA)
b: STATISTIC FOR GENERAL ASSOCIATIONS OF NOMINAL CATEGORICAL VARIABLES CONTROLLING FOR CENTER

TABLE 23
LSH
SLEEP HISTORY AT RANDOMIZATION

VARIABLE	PLACEBO N=54	10MG N=45	15MG N=46	OVERALL N=145	ANOVA P VALUE
USUAL SLEEP MEAN LATENCY SCORE (a) [SD]	4.3 [0.9]	4.1 [1.0]	4.1 [1.0]	4.2 [1.0]	0.608
USUAL SLEEP MEAN TIME SCORE (b) [SD]	2.4 0.5	2.4 0.5	2.4 0.5	2.4 [0.5]	0.698+
NO. OF (%) OF PATIENTS WITH PREVIOUS HYPNOTIC	1(2%)	1(2%)	1(2%)	3(2%)	1.000 c

+: SIGNIFICANT TREATMENT BY CENTER INTERACTION.
(a): SCALE: 1=<15 MIN, 2=15-29, 3=30-44, 4=45-49, 5=>60 MIN. NO PATIENT CHECKED 1 OR 2.
(b): SCALE: 1=<4 HRS, 2=4-5, 3=5-6, 4=6-7, 5=>7 HRS. NO PATIENT CHECKED 1, 4 OR 5.
c: EXACT TEST.

TABLE 24

SUMMARY OF PRIMARY EFFICACY RESULTS+

VARIABLE	WEEK	PLACEBO	10MG	15MG	P-VALUE
SUBJECTIVE SLEEP LATENCY (MIN)	BASELINE	58.2	65.1	75.9	0.325
	2	61.0	34.5*	38.1*	0.004
	3	49.7	34.0*	33.1*	0.026
	4	60.7	32.0*	33.4*	0.005
	5	42.8	26.8*	33.0	0.039
	POST Tt	45.7	53.9	69.9	0.384
	POST Tt day 1	52.9	64.4	94.2	0.291
SUBJECTIVE TOTAL SLEEP TIME (MIN)	BASELINE	315	316	308	0.975
	2	331	337*	378*	0.005
	3	348	373	384 @	0.060
	4	344	375	375	0.077
	5	360	390	385	0.229
	POST Tt	359	354	332	0.172
	POST Tt day 1	342	332	295 @	0.068
SUBJECTIVE NO. OF AWAKENINGS	BASELINE	2.6	2.5	2.7	0.916
	2	2.1	1.2*	1.5*	0.001
	3	1.9	1.4	1.2*	0.032
	4	1.7	1.2	1.3	0.122
	5	1.7	1.4	1.9	0.172
	POST Tt	1.9	1.7	1.9	0.821
	POST Tt day 1	2.0	1.8	2.0	0.991
SLEEP QUALITY (a)	BASELINE	3.0	2.9	3.2	0.204
	2	3.0	2.3*	2.4*	0.001
	3	2.8	2.5	2.4*	0.035
	4	2.7	2.3 a	2.4@	0.076**
	5	2.6	2.4	2.4	0.479**
	POST Tt	2.7	2.8	2.9 @	0.070
	POST Tt day 1	2.8	2.9	3.0	0.211
MORNING SLEEPINESS SCORE	BASELINE	54.2	46.3	45.2	0.145
	2	57.0	60.0	53.8	0.576
	3	59.0	61.4	57.3	0.709
	4	62.6	63.8	60.0	0.645
	5	63.5	63.2	54.8@	0.066
	POST Tt	62.1	57.6@	48.9*	0.005+

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO, P<0.05
@: DIFFERENT From PLACEBO, P<0.10
(a): SCALE: 1=EXCELLENT, 2=GOOD, 3=FAIR, 4=POOR
**: SIGNIFICANT TREATMENT BY CENTER INTERACTION, P<0.05
ANALOG SCALE:
+: LOCF ANALYSIS ON INTENT-TO-TREAT DATA SET

TABLE 25
LSH
BASELINE MEANS & MEAN CHANGES
FROM BASELINE IN SUBJECTIVE SLEEP LATENCY
(MINS)

WEEK		PLACEBO	10MG	15MG	P-VALUE@
BASELINE (b)	MEAN	58.8	61.1	67.1	0.590
	SE	8.5	7.9	11.0	
	N	44.0	37	37	
2	MEAN	2.0	-30.0*	-31.3*	<0.001
	SD	47.3	43.1	52.6	
	N	52	41	42.0	
3	MEAN	-7.8	-28.5*	-36.3+	0.003
4	MEAN	2.8	-30.4*	-36.9*	<0.001
	SD	74.1	48.8	64.9	
	N	47	38	41	
5	MEAN	-16.3	-33.7*	-34.1	0.036
	SD	34.8	45.8	53.5	
	N	45	37	37	
POST Tt	MEAN	-14.1	-8.4	0.7	0.075
	SD	36.9	55.6	78.9	
	N	44	37	37	

*: SIGNIFICANTLY DIFFERENT FROM PLACEBO, P<0.05
@: ANALYSIS PERFORMED USING LOGARITHM AND TREATING CENSORED VALUES AS UNCENSORED
(b): BASELINE FOR PATIENTS WHO ALSO HAD POST TREATMENT DATA

TABLE 26
TOLERANCE TO TREATMENT: SUBJECTIVE
SLEEP LATENCY AND TOTAL SLEEP TIME
CHANGE FROM WEEK 2 TO WEEK 5(a)
LSH

VARIABLE		PLACEBO	10MG	15MG	P-VALUE
SUBJECTIVE	MEAN	-10.5 c	-4.7 c	-4.2	0.206
SLEEP	SD	31.5	12.6	18.2	
LATENCY (b)	N	45	37	37	
(MINS)					
SUBJECTIVE	MEAN	20.5 c	11.3	2.7	0.414
TOTAL SLEEP TIME	SD	61.4	53.4	54.9	
(MINS)					

(a): CHANGE EQUALS WEEK 5 VALUE MINUS WEEK 2 VALUE.
(b). ANALYSIS OF LATENCY PERFORMED USING LOGARITHM OF DATA VALUES.
c: SIGNIFICANTLY DIFFERENT FOR ZERO, P<0.05.

TABLE 27
SUBJECTIVE SLEEP LATENCY (MIN): M AN CHANGE
FROM BASELiNE PLACEBO PERIOD TO THE
POST TREATMENT WEEK
LSH

POST TREATMENT DAY		PLACEBO	10MG	15MG	P-VALUE (a)
BASELINE	MEAN	58.8	61.1	67.1	0.590
	N	44	37	37	
1	MEAN	-7.0 b	2.5 c	30.5	0.554
	N	44	36	36	
2	MEAN	-14.8 b	-13.7 b	-5.1**	0.100
	N	44	35	37	
3	MEAN	-8.3 b	-7.4 b	-9.0	0.854
	N	44	36	37	
4	MEAN	-26.5 b	-11.2 b	-12.3 c	0.131
	N	43	35	37	
OVERALL	MEAN	-14.1 b	-8.4 c	0.7	0.275
	N	44	37	37	

(a): ANALYSIS PERFORMED USING LOGARITHM OF DATA VALUES . VALUES IN THE TABLE ARE NOT TRANSFORMED AND GIVE MEANS OF DIFFERENCE: POST TREATMENT VALUE MINUS BASELINE VALUE.
b: SIGNIFICANTLY DIFFERENT FROM ZERO, P<0.05
c: DIFFERENT FROM ZERO, P<0.10
**: DIFFERENT FROM 10MG, P<0.10.

TABLE 28
DAILY MEAN SUBJECTIVE TOTAL SLEEP TIME (MIN) DURING THE POST TREATMENT WEEK
LSH

POST TREATMENT DAY		PLACEBO	10MG	15MG	P-VALUE
1	MEAN	342	332	295 @	0.068
	SD	106	114	130	
	N	44	36	36	
2	MEAN	375	376	346	0.281
	SD	89	121	105	
	N	44	35	37	
3	MEAN	355	363	334	0.346
	SD	93	99	99	
	N	44	36	37	
4	MEAN	366	344	359	0.321
	SD	85	121	39	
	N	43	36	37	
OVERALL	MEAN	359	354	332	0.172
	SD	76	83	86	
	N	44	37	37	

@: DIFFERENT FROM PLACEBO, P<0.10.

TABLE 29
BASELINE SUBJECTIVE TOTAL SLEEP TIME (MIN)
AND MEAN CHANGE FROM THE BASELINE
PLACEBO PERIOD TO THE POST TREATMENT WEEK
LSH

POST-TREATMENT DAY		PLACEBO	10MG	15MG	P-VALUE(x)
BASELINE a	MEAN	319.1	321.0	324.8	0.672
	SD	84.2	86.8	72.9	
	N	44	36	36	
1	MEAN	23.0	14.1	-30.2*#	0.023
	SD	109.4	121.9	121.6	
	N	44	36	36	
2	MEAN	55.9 b	53.9 b	18.7 @	0.072
	SD	77.3	116.8	101.2	
	N	44	35	37	
3	MEAN	35.4 b	40.3 c	6.8	0.129
	SD	78.5	120.9	102.8	
	N	44	36	37	
4	MEAN	46.2 b	21.0	34.4 b	0.468
	SD	74.44	122.5	87.6	
	N	43	36	37	
OVERALL	MEAN	40.2 b	33.2 b	7.4*	0.041
	SD	66.4	91.2	81.9	
	N	44	37	37	

*: SIGNIFICANT DIFFERENCE BETWEEN PLACEBO AND 15MG, P<0.05.
@: DIFFERENT BETWEEN PLACEBO AND 15MG, P<0.10.
*#: SIGNIFICANTLY DIFFERENT FROM 10MG, P<0.05.
a: FOR PATIENTS WHO ALSO HAD DATA ON POST TREATMENT DAY 1
b: SIGNIFICANTLY DIFFERENT FROM ZERO, P<0.05.
c: DIFFERENT FROM ZERO, P<0.10.
(x): OVERALL TREATMENT COMPARISON BETWEEN TREATMENT GROUPS.

NOTE: TABLUATED VALUES GIVE THE MEAN OF THE DIFFERENCES:
POST TREATMENT VALUE MINUS BASELINE VALUE.

TABLE 30
MEAN NUMBER OF AWAKENINGS AND SLEEP QUALITY
AND MEAN CHANGE FROM BASELINE
DURING FIRST DAY OF THE POST TREATMENT WEEK
LSH

VARIABLE		PLACEBO	10MG	15MG	P-VALUE (x)
NUMBER OF AWAKENINGS	MEAN	2.0	1.8	2.0	0.991
	SD	1.4	1.4	1.9	
	N	44	35	35	
	MEAN b	-0.4 a	-0.7 a	-0.5	0.750
	SD	1.4	1.9	1.8	
SLEEP QUALITY c	MEAN	2.8	2.9	3.0	0.211
	SD	0.9	1.0	1.1	
	N	44	36	36	
	MEAN b	-0.1	0.0	-0.1	0.82
	SD	1.0	1	1.1	

a: SIGNFICANTLY DIFFERENT FROM BASELINE, P<0.05.
b: MEAN OF THE DIFFERENCE: POST TREATMENT VALUE
MINUS BASELINE VALUE.
c: SCALE: 1=EXCELLENT, 2=GOOD, 3=FAIR, 4=POOR
(x): OVERALL TREATMENT COMPARISON AMONG TREATMENT GROUPS.

TABLE 31
DAILY MEAN MORNING SLEEPINESS DURING
POST TREATMENT WEEK
LSH

POST TREATMENT DAY		PLACEBO	10MG	15MG	P-VALUE (x)
1	MEAN	58.8	052.7	40.4*	0.006
	SD	30.7	33.8	32.1	
	N	44	36	36	
2	MEAN	65.1	59.9	51.8*	0.018 a
	SD	27.6	31.7	27.5	
	N	44	35	37	
3	MEAN	61.8	62.3	48.8*	0.014 a
	SD	28.2	28.7	25.7	
	N	44	36	37	
4	MEAN	63.4	56.5 @	55.3 @	0.061 a
	SD	25.6	31.0	24.0	
	N	43	36	37	
OVERALL	MEAN	62.1	57.6 @	48.9*	0.005 a
	SD	24.2	25.5	22.8	
	N	44	37	37	

*: SIGNIFICANT DIFFERENT FROM PLACEBO , P<0.05.
@: DIFFERENT FROM PLACEBO, P<0.10.
a: SIGNIFICANT TREATMENT BY CENTER INTERACTION, P<0.05.
(x): OVERALL COMPARISON AMONG TREATMENT GROUPS.
SCALE: 0MM=VERY SLEEPY, 100MM=NOT AT ALL SLEEPY.

TABLE 32
MORNING SLEEPINESS: MEAN CHANGE FROM THE
BASELINE PLACEBO PERIOD TO POST TREATMENT WEEK a
LSH

POST TREATMENT DAY		PLACEBO	10MG	15MG	P-VALUE (x)
BASELINE	MEAN	52.9	48.7	44.4	0.284
	SD	26.7	27.2	22.7	
	N	44	37	37	
1	MEAN	05.9	4.4	-4.7@	0.092
	SD	30.2	28.4	32.1	
	N	44	36	36	
2	MEAN	12.2 b	10.3 c	7.4	0.145 d
	SD	30.2	30.4	29.4	
	N	44	35	37	
3	MEAN	8.8 b	13.3 b	4.3	0.224
	SD	27.8	31.3	26.5	
	N	44	36	37	
4	MEAN	9.6 b	07.4	10.9 b	0.715
	SD	28.9	30.9	25.8	
	N	43	36	37	
OVERALL	MEAN	9.2	8.9	4.5	0.296
	SD	25.5	23.9	23.9	
	N	44	37	37	

@: DIFFERENT FROM PLACEBO, P<0.10.
a: MEAN OF DIFFERENCE: POST REATMENT MINUS BASELINE VALUE
b: SIGNIFICANTLY DIFFERENT FROM ZERO, P<0.05.
c: DIFFERENT FROM ZERO, P<0.10.
d: SIGNFINICANT TREATMENT BY CENTER INTERACTION, P<0.05.
(x): OVERALL TREATMENT COMPARISON AMONG TREATMENT GROUPS.

Table 33
LSH
Summary of Primary and Secondary Efficacy
Results by Reviewer (Means)

Variable	Week	Placebo	10mg (p-value)*	15mg (p-value)*	**p-Value
Subjective Sleep Latency (Mins.)	Baseline	58.2	64.7	75.9	0.5255
	2	60.2	34.5*(.0026)	38.1*(0.0183)	0.0054
	3	49.7	34.0*(.0090)	33.1*(0.0419)	0.0196
	4	60.7	32.0*(0.0031)	33.4*(0.0224)	0.0063
	5	42.8	26.8*(0.0117)	33.0	0.0164
	Post Tt	45.7	52.1	67.9	0.2130
Subjective Total Sleep Time	Baseline	315.0	323.9	327.3	0.5540
	2	333.4	385.4*(0.0039)	377.3*(0.0192)	0.0068
	3	345.8	371.5	378.4*(0.0337)	0.0788
	4	355.9	376.1	384.5	0.1468
	5	359.4	383.2	358.8	0.2927
	Post Tt	365.2	360.9	345.5	0.6759
Subjective Number of Awakenings	Baseline	002.5	2.2	2.4	0.5191
	2	2.0	1.2*(0.0079)	1.4@(0.0547)	0.0182
	3	1.8	1.4	1.3*(0.0476)	0.0999
	4	1.8	1.3	1.3	0.2135
	5	1.7	1.4	01.4	0.4921
	Post Tt	1.8	1.6	1.9	0.6962
Subjective Sleep Quality a	Baseline	3.0	2.8	3.0	0.3699
	2	2.9	2.3*(0.001)	2.4*(0.0036)	0.0002
	3	2.8	2.5	2.3*(0.0114)	0.0313
	4	2.6	2.3	2.3	0.1693
	5	2.6	2.5	2.6	0.6217
	Post Tt	2.6	2.7	2.8@(0.0916)	0.2084

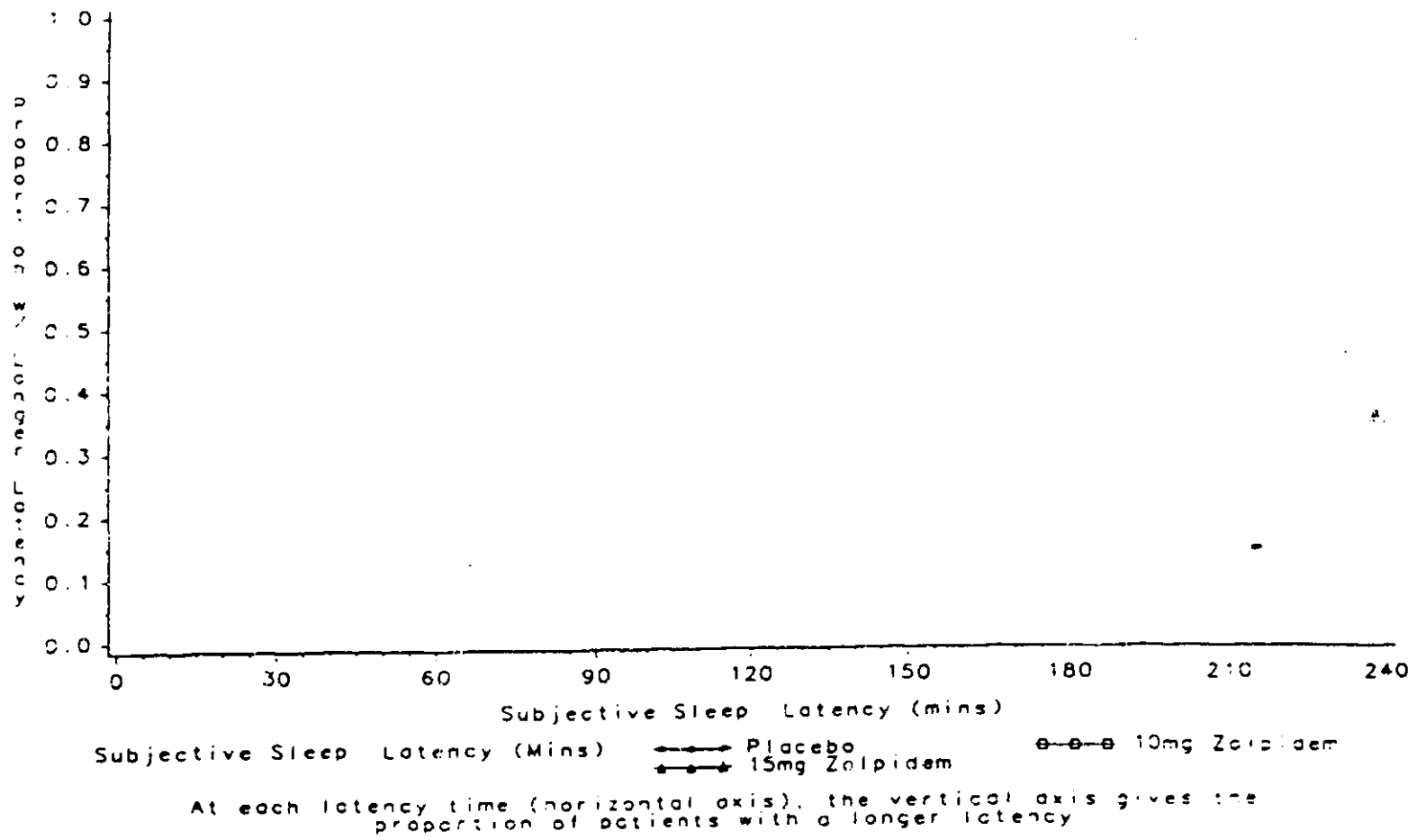
Table 33
LSH
Summary of Primary and Secondary Efficacy
Results by Reviewer (Means)
(continued)

Variable	Week	Placebo	10mg (p-value)	15mg (p-value)	**p-Value
Subjective Morning Sleepiness b	Baseline	54.0	48.3	46.9	0.4000
	2	60.0	62.2	53.9	0.2648
	3	59.7	59.9	58.2	0.9231
	4	62.9	64.8	59.3	0.6129
	5	62.4	61.7	50 2*(0.0229)	0.0421
	Post Tt	63.2	59.4	52.0*(0.0387)	0.1353

*: Significantly different from placebo; $p < 0.05$.
**: Overall p-value
@: Different from placebo, $p < 0.10$.
a: Scale: 1 = excellent, 2 = good, 3 = fair, 4 = poor
b: Analog scale: 0mm = very sleepy, 100mm = not at all sleepy.
Note: No p-value means that the 10mg and 15mg treatment groups are not significantly different from placebo.

Figure 1

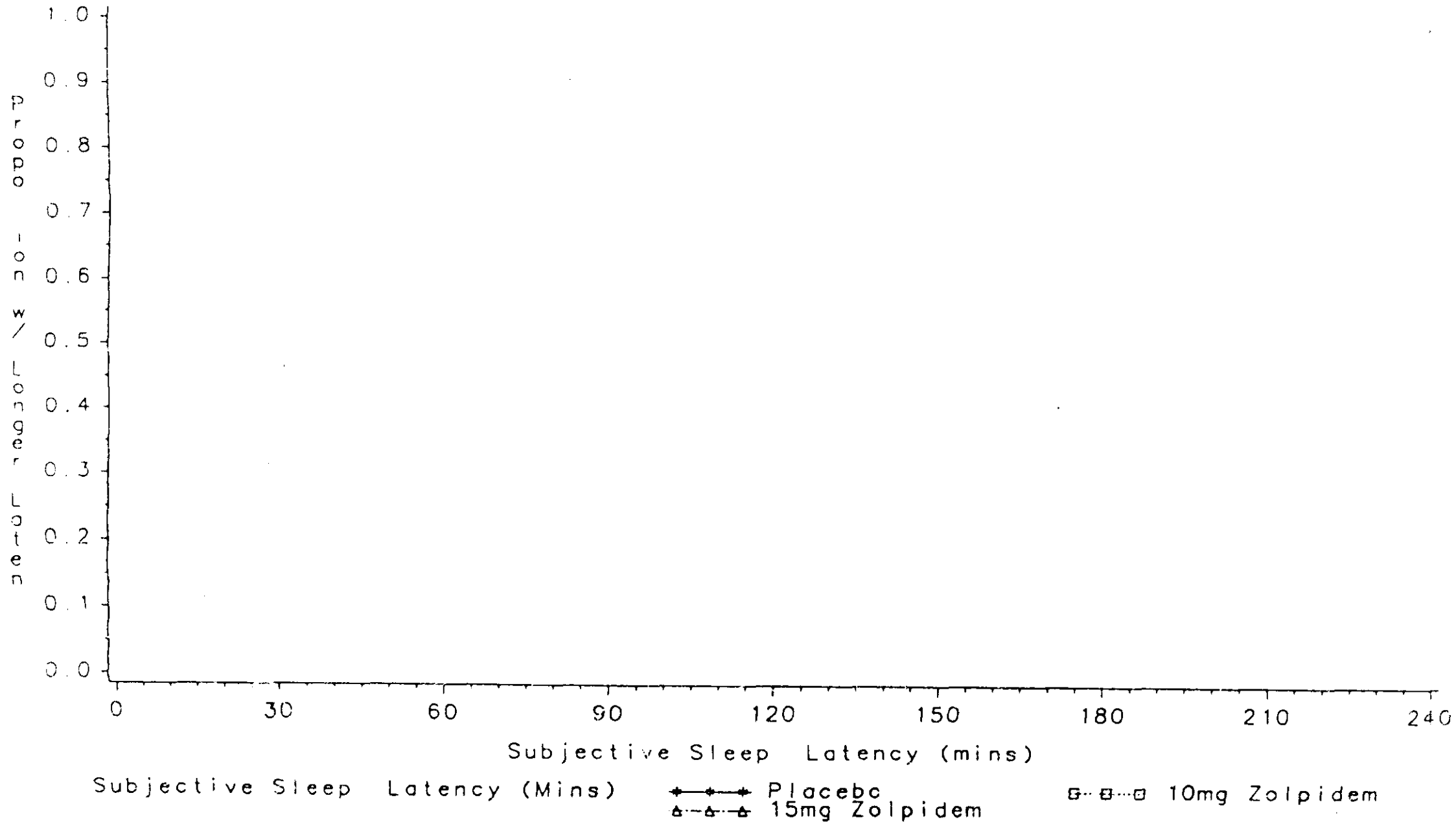
Product-Limit Estimates of Subjective
Sleep Latency (Minutes) During Week 2, by Treatment
LSH



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

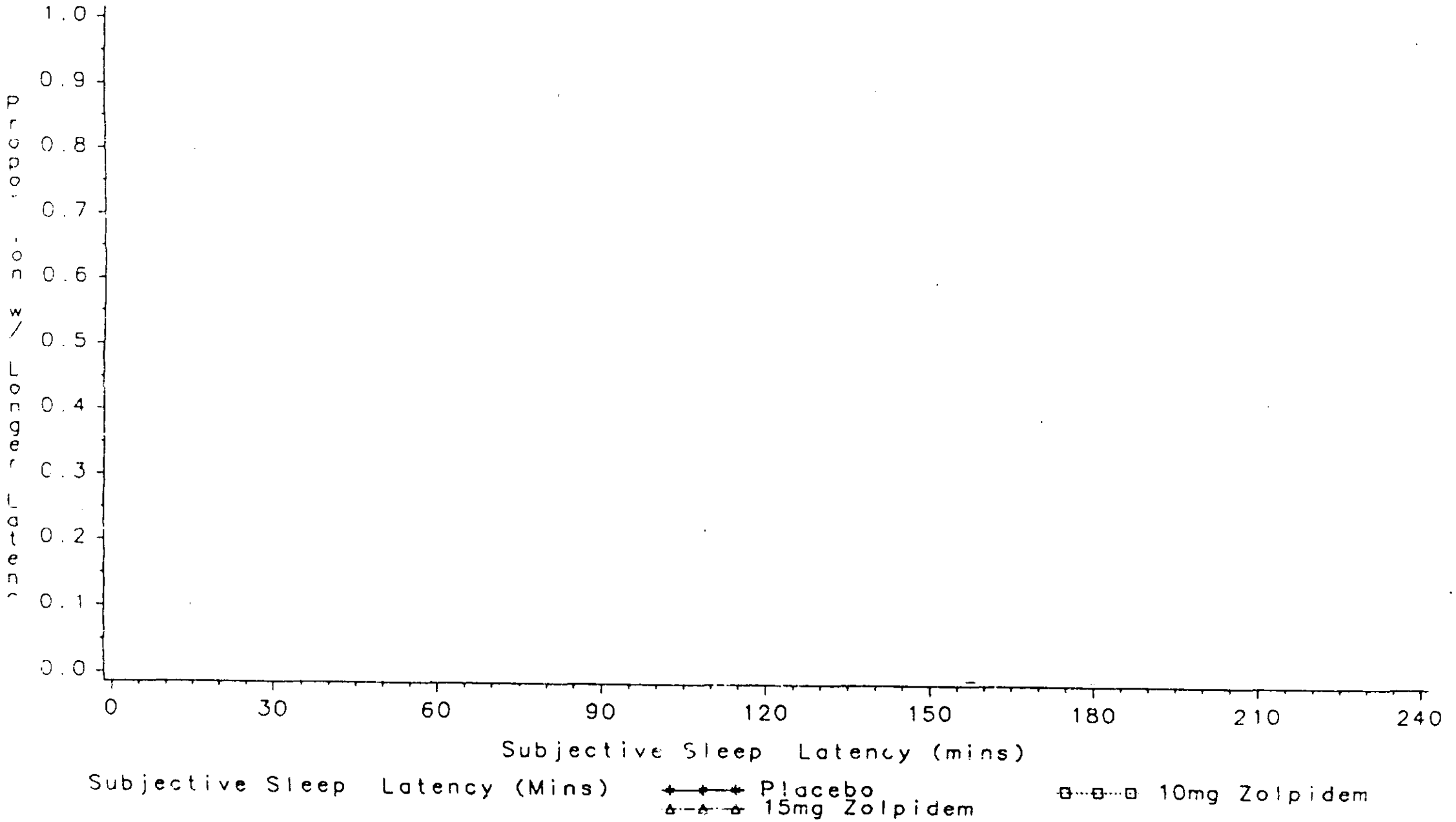
Product Limit Estimates – Subjective Sleep Latency (Minutes) Analysis
By Treatment
Baseline Placebo Period



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

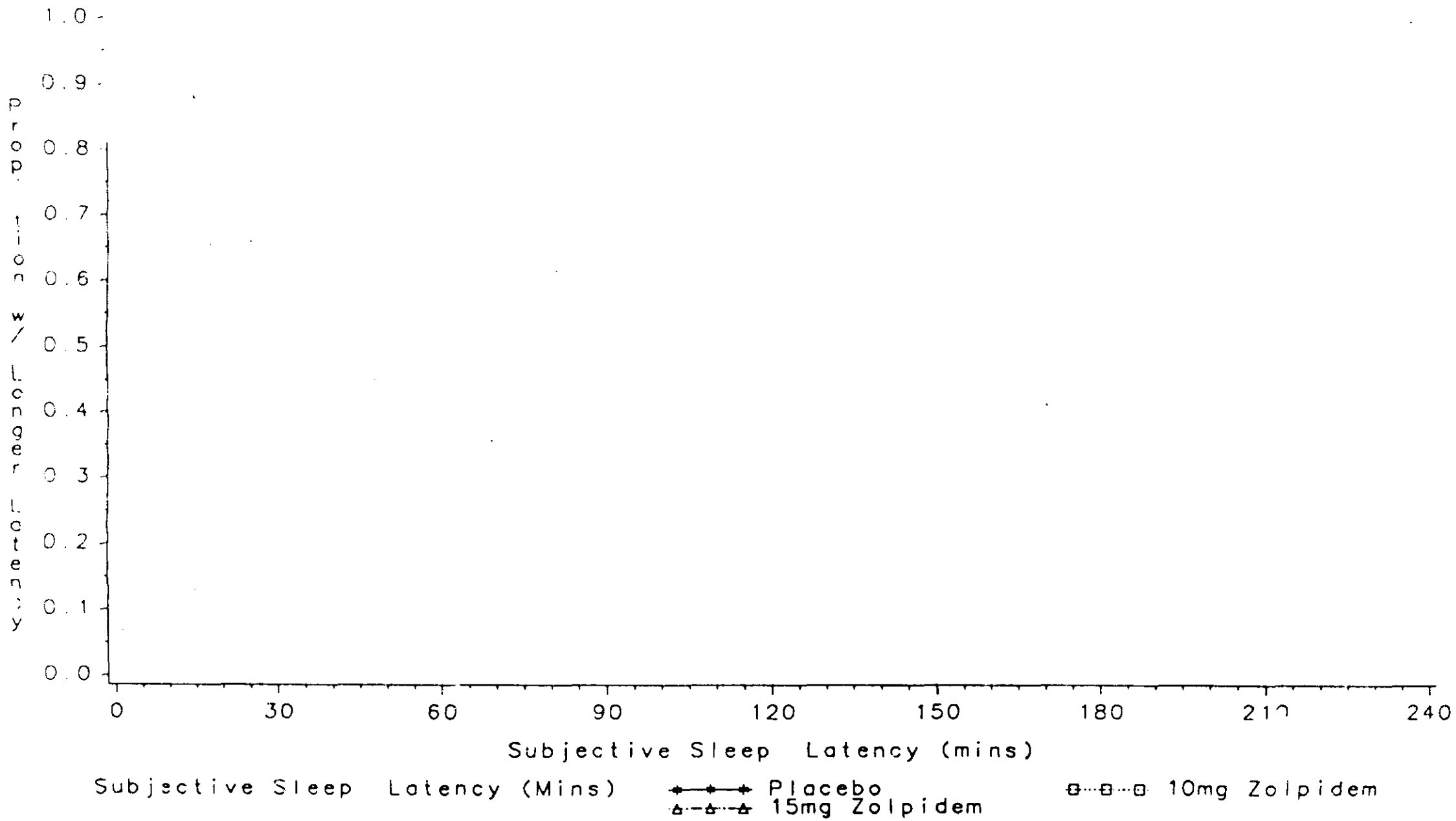
Product Limit Estimates – Subjective Sleep Latency (Minutes) Analysis
By Treatment
Week 2



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

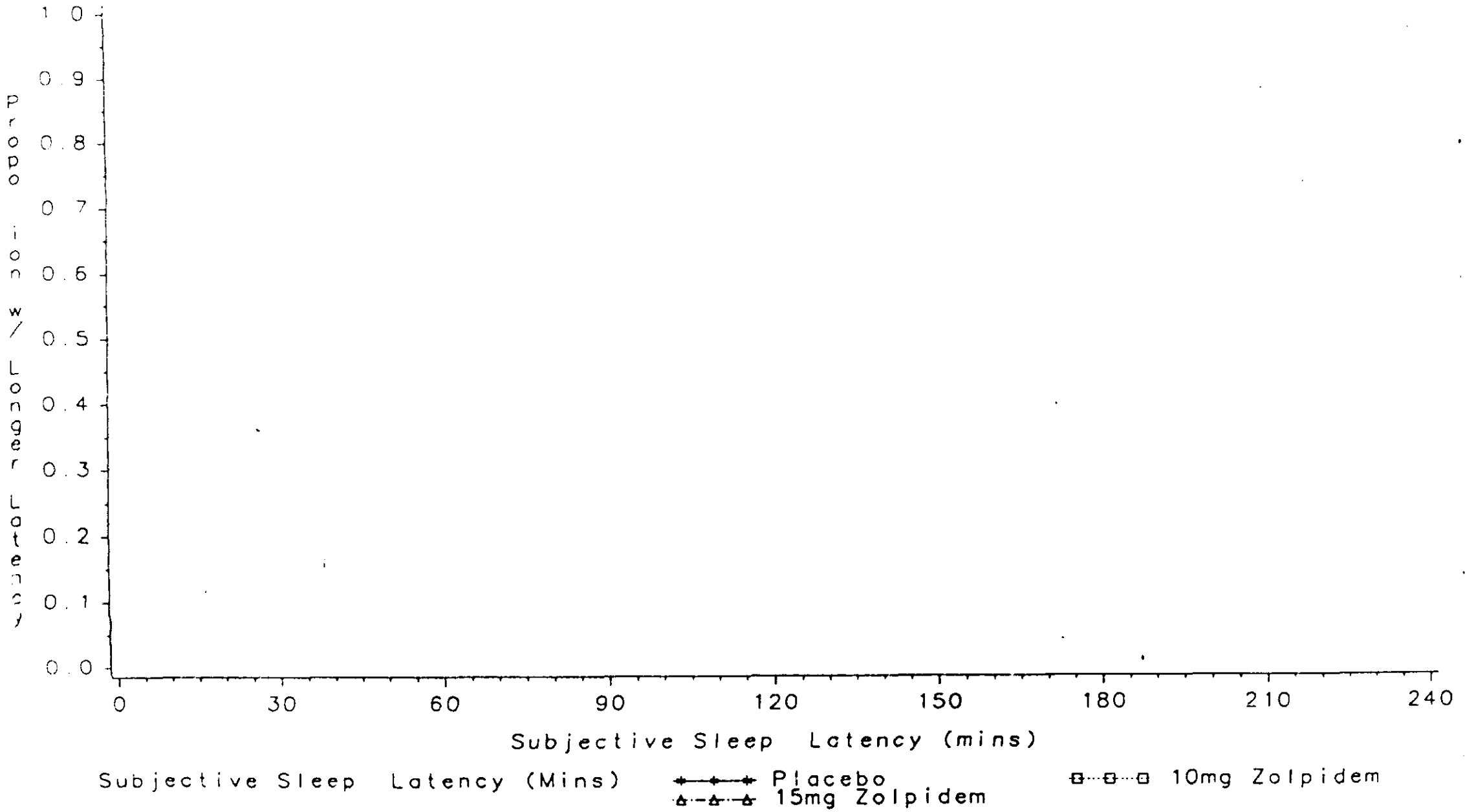
Product Limit Estimates – Subjective Sleep Latency (Minutes) Analysis
By Treatment
Week 3



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

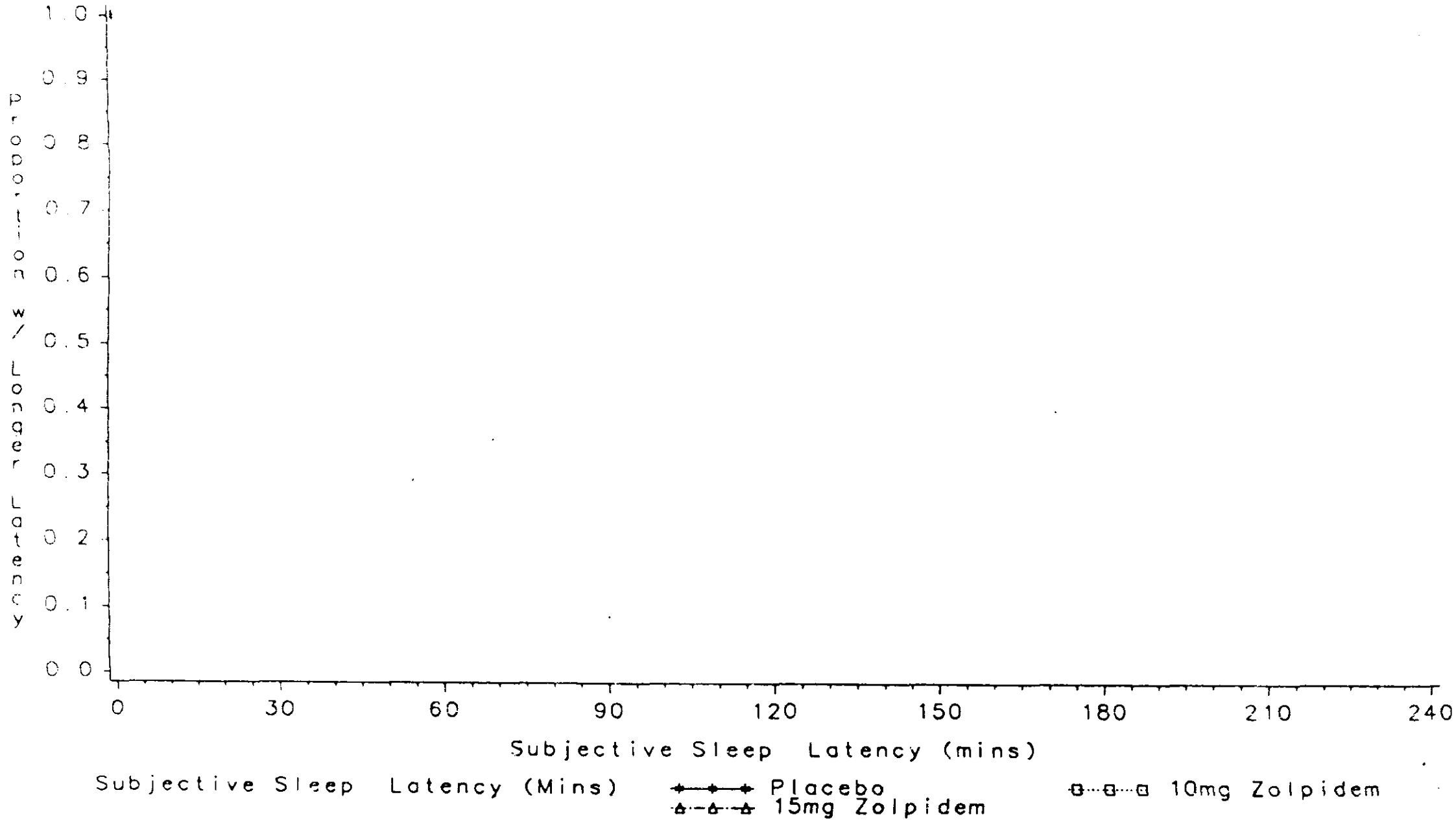
Product Limit Estimates - Subjective Sleep Latency (Minutes) Analysis
By Treatment
Week 4



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

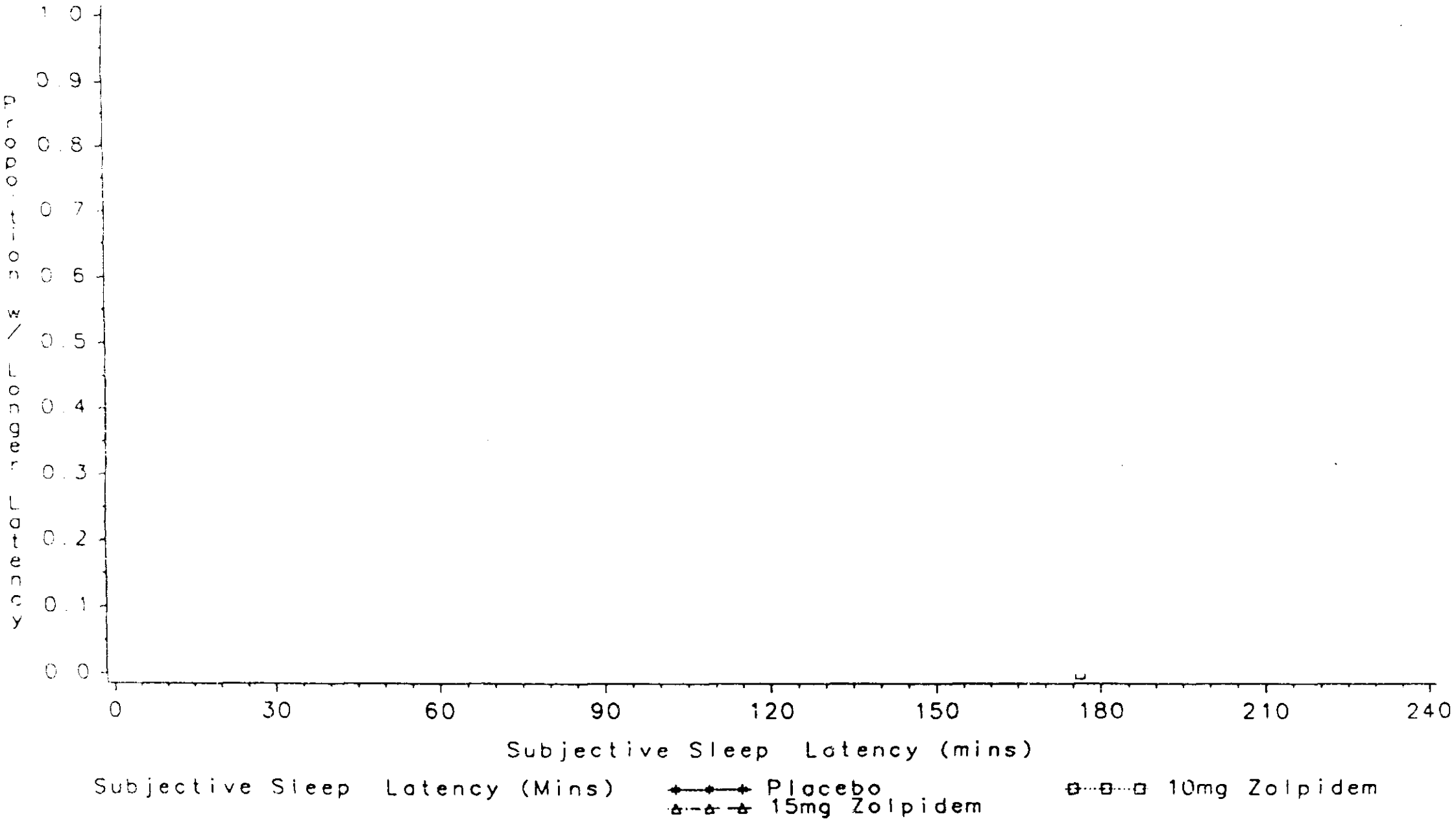
Product Limit Estimates Subjective Sleep Latency (Minutes) Analysis
By Treatment
Week 5



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

Product Limit Estimates - Subjective Sleep Latency (Minutes) Analysis
By Treatment
Placebo Post-Treatment Week



At each latency time (horizontal axis), the vertical axis gives the proportion of patients with a longer latency

Figure 2

LSH PRODUCT LIMIT ESTIMATES BY INVESTIGATOR
BASELINE PERIOD
SUBJECTIVE SLEEP LATENCY

CUMULATIVE PROPORTION SURVIVING GROUP VAR: INVNBR

A IS Docherty/Kann B IS Fillingim C IS Lahmeyer D IS Cobb
E IS Lappin

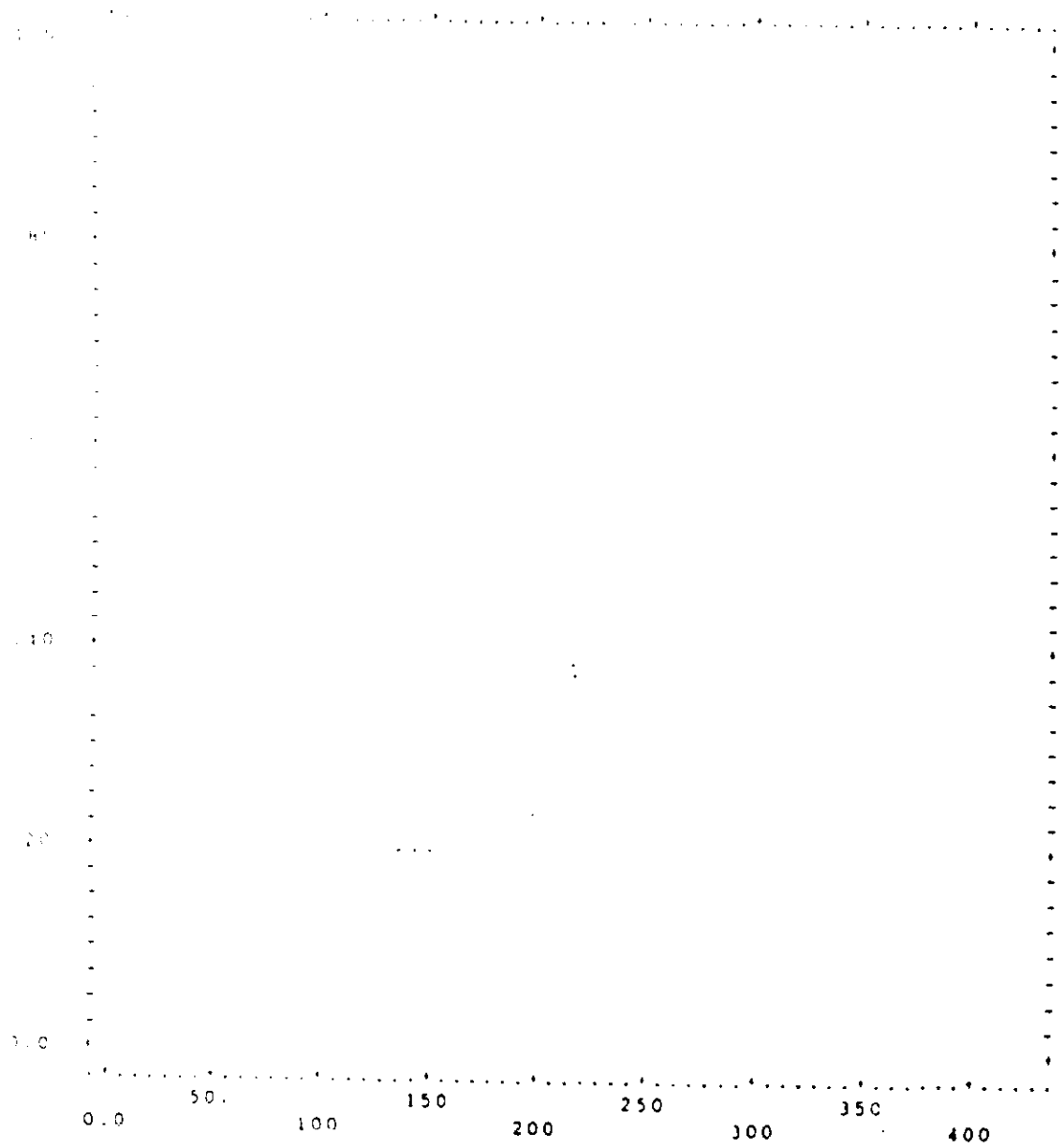


Figure 2

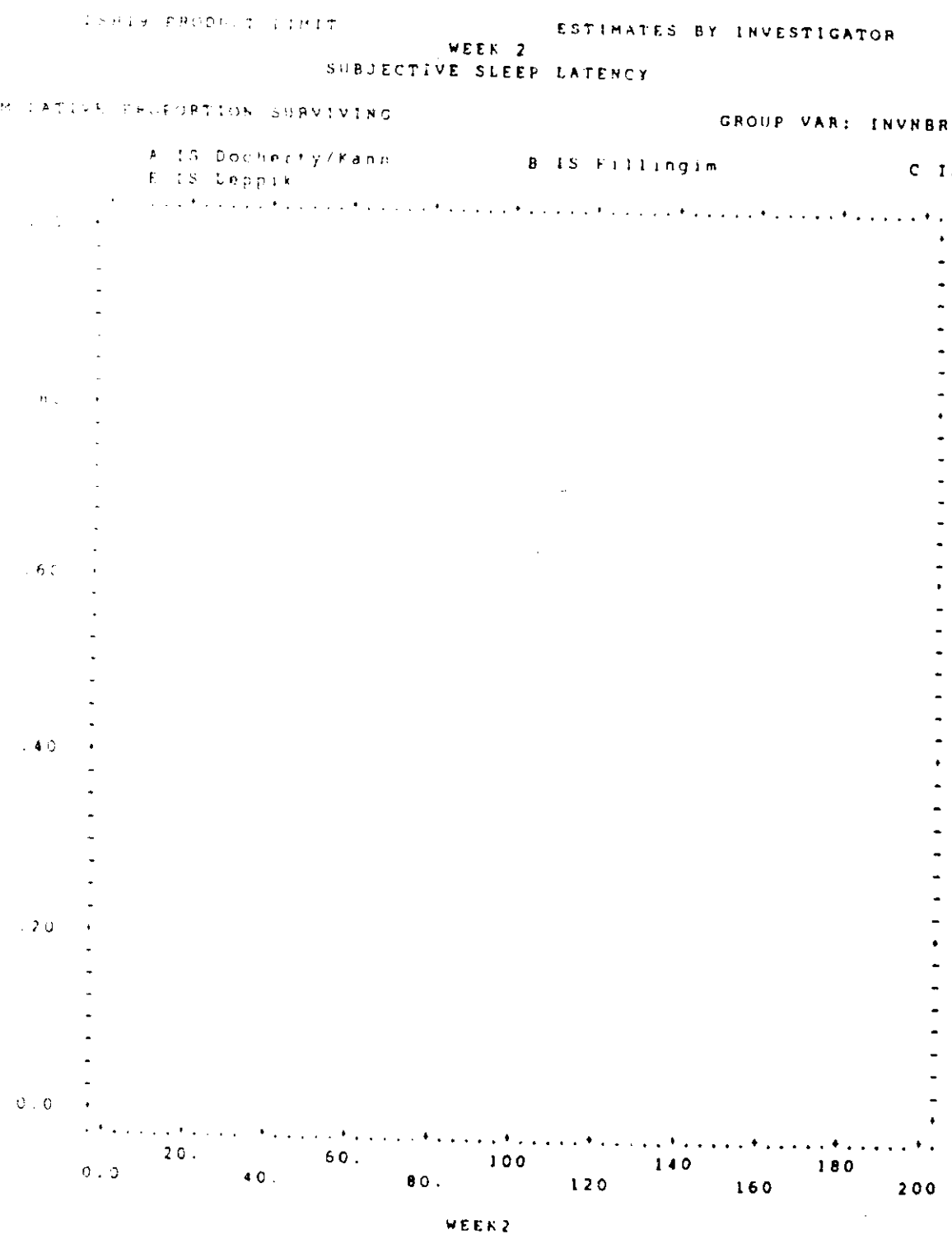

PRODUCT LIMIT ESTIMATES BY INVESTIGATOR
WEEK 2
SUBJECTIVE SLEEP LATENCY
CUMULATIVE PROPORTION SURVIVING
GROUP VAR: INVNBR
A IS Docherty/Kann
B IS Fillingim
C IS Lahmeyer
D IS Cohn
E IS Leppik
.60
.40
.20
0.0
0.0
20.
40.
60.
80.
100
120
140
160
180
200
WEEK2

Figure 2

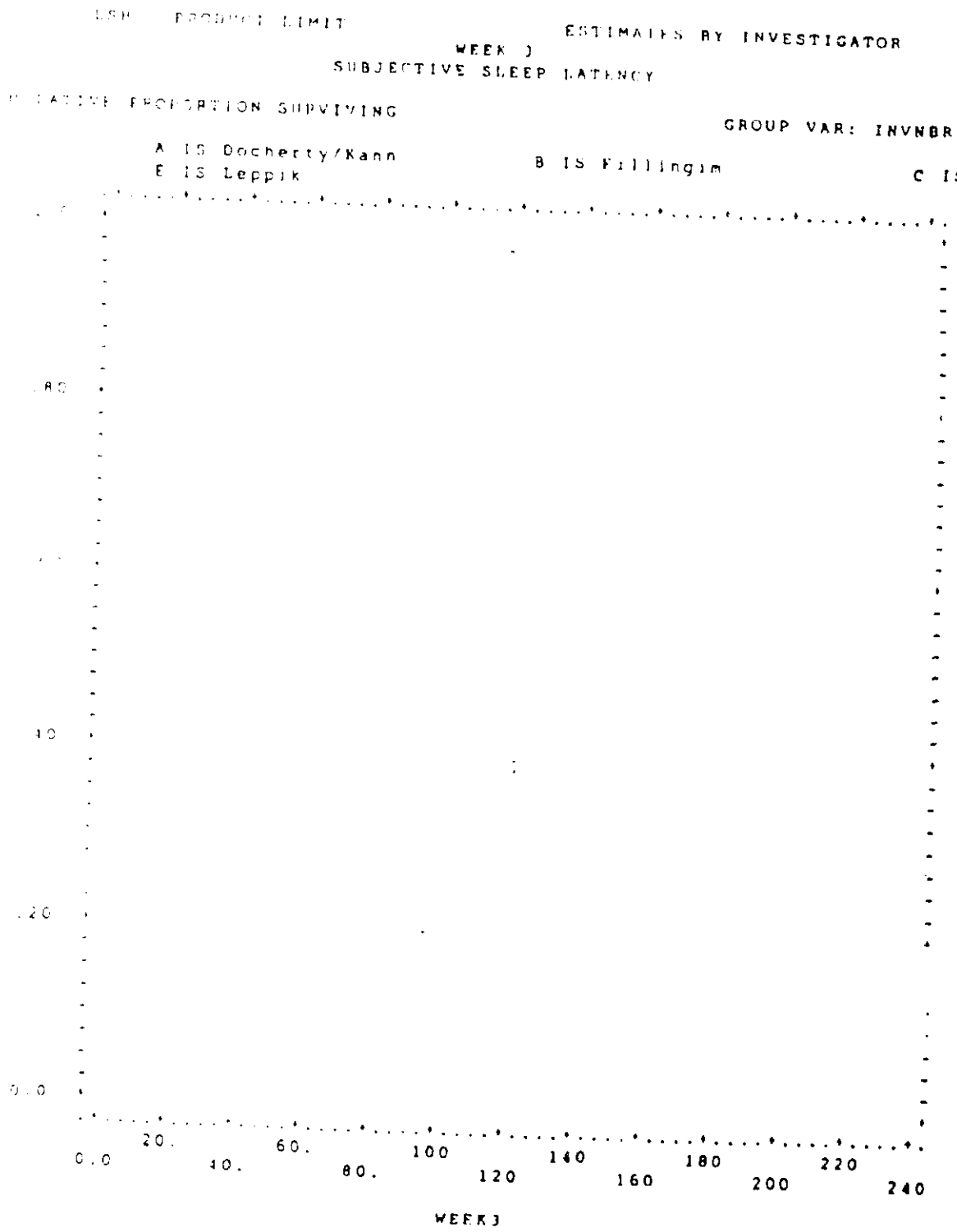

LSH PRODUCT LIMIT ESTIMATES BY INVESTIGATOR
WEEK)
SUBJECTIVE SLEEP LATENCY
CUMULATIVE PROPORTION SURVIVING
GROUP VAR: INVNBR
A IS Docherty/Kann
B IS Fillingim
C IS Lahmeyer
D IS Cohn
E IS Leppik
.80
.40
.20
0.0
0.0
20.
40.
60.
80.
100
120
140
160
180
200
220
240
WEEKS

Figure 2

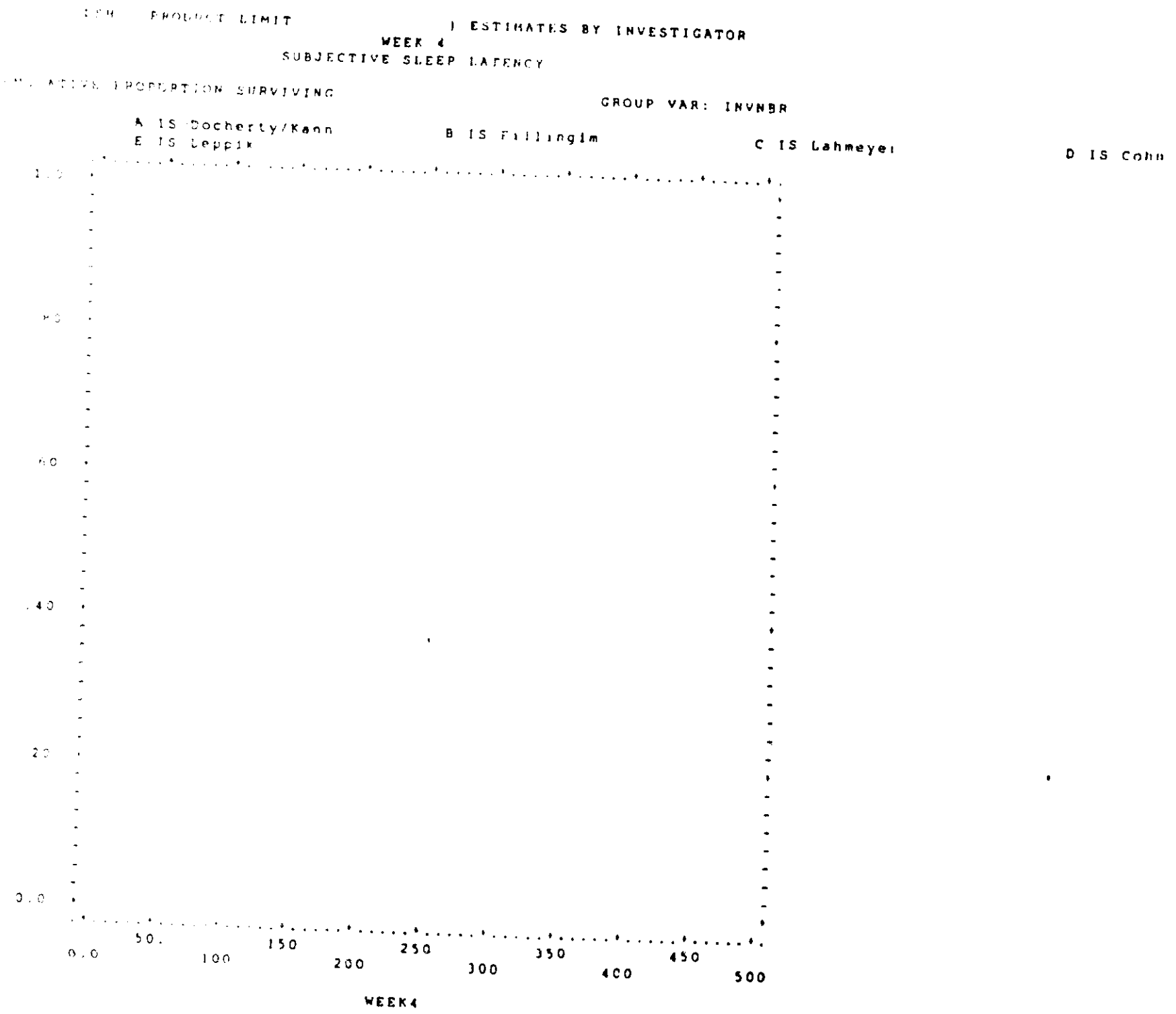

PRODUCT LIMIT ESTIMATES BY INVESTIGATOR
WEEK 4
SUBJECTIVE SLEEP LATENCY
PROPORTION SURVIVING
GROUP VAR: INVNBR
A IS Docherty/Kann
B IS Fillingim
C IS Lahmeyer
D IS Cohn
E IS Leppik
1.0
.80
.60
.40
.20
0.0
0.0
50.
100
150
200
250
300
350
400
450
500
WEEK4

Figure 2

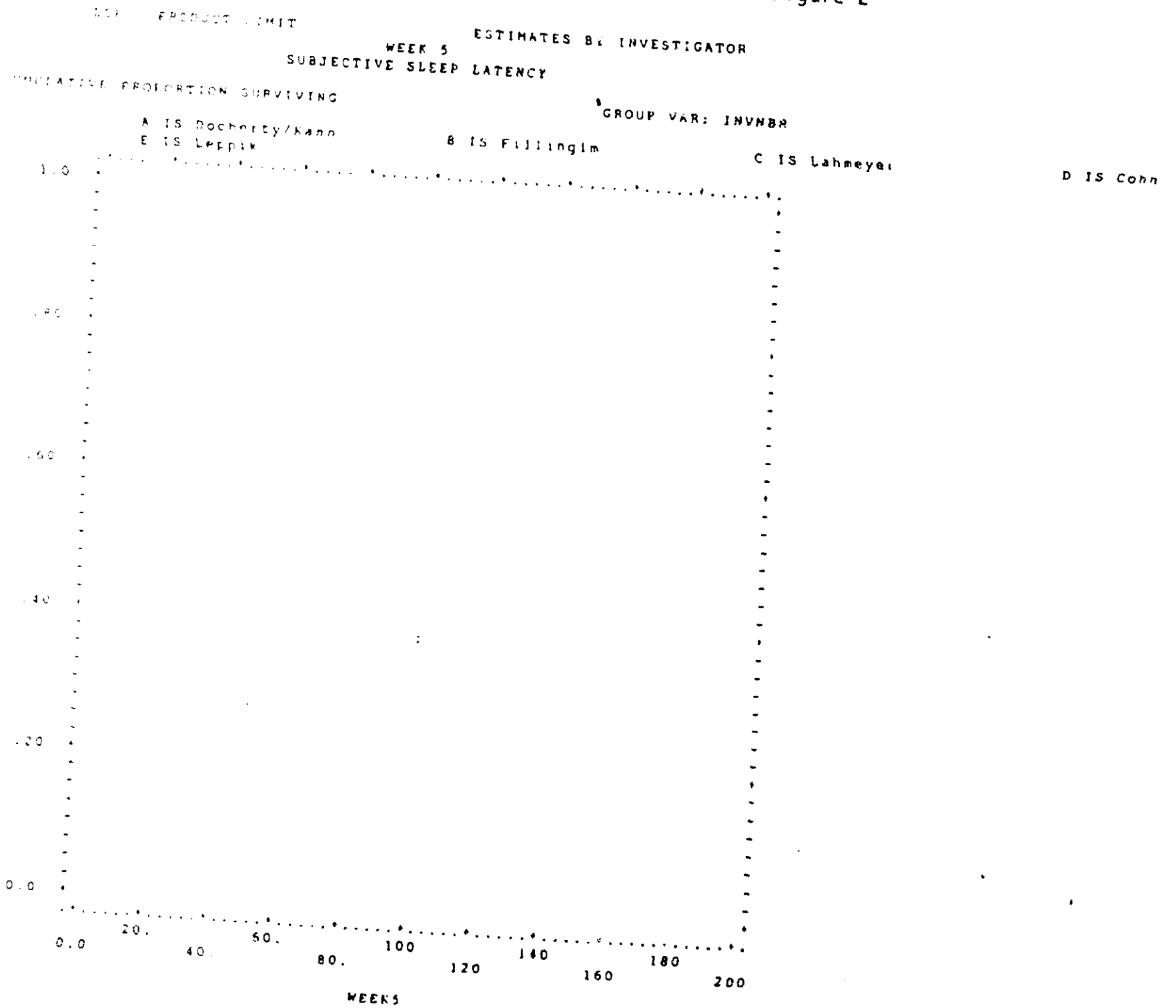
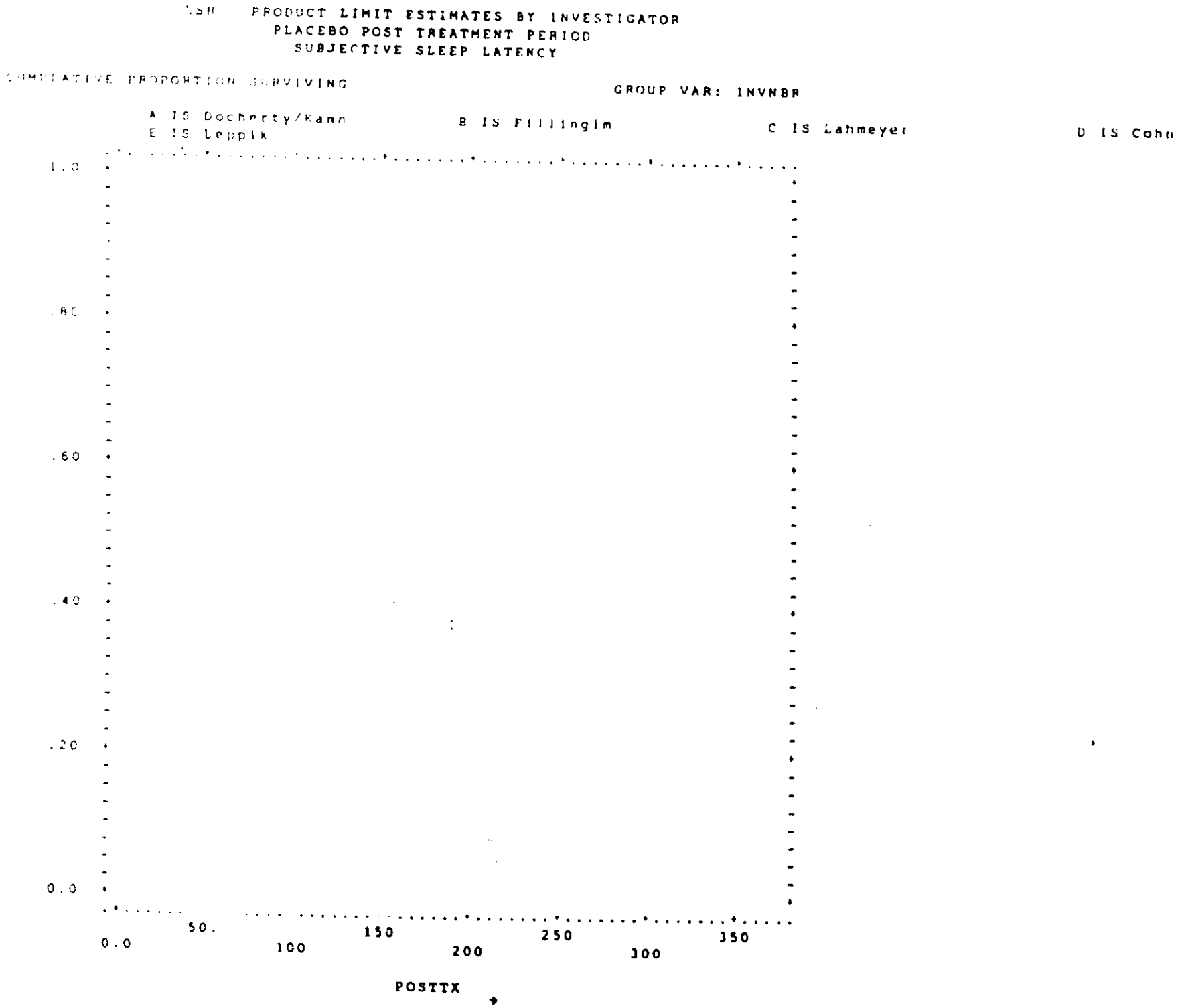

PRODUCT LIMIT ESTIMATES BY INVESTIGATOR
WEEK 5
SUBJECTIVE SLEEP LATENCY
CUMULATIVE PROPORTION SURVIVING
GROUP VAR: INVNBR
A IS Docherty/Kapp
B IS Fillingim
C IS Lahmeyer
D IS Conn
E IS Leppik
1.0
.80
.60
.40
.20
0.0
0.0
20.
40.
60.
80.
100
120
140
160
180
200
WEEKS

Figure 2


PRODUCT LIMIT ESTIMATES BY INVESTIGATOR
PLACEBO POST TREATMENT PERIOD
SUBJECTIVE SLEEP LATENCY
CUMULATIVE PROPORTION SURVIVING
GROUP VAR: INVNBR
A IS Docherty/Kann
B IS Fillingim
C IS Lahmeyer
D IS Cohn
E IS Leppik
1.0
.80
.60
.40
.20
0.0
0.0
50.
100
150
200
250
300
350
POSTTX