CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-774

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21,774/N-000
Name of drug:	Ambien CR (zolpidem MR)
Indication:	primary insomnia
Applicant:	Sanofi-Synthelabo
Dates:	Received 6/8/04; PDUFA 4/8/05
Review priority:	S
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Joan Buenconsejo
Concurring reviewers:	Thomas Permutt, Ph.D.
Biometrics Division Director	S. Edward Nevius, Ph.D.
Medical division:	HFD 170
Clinical team:	D. Elizabeth McNeil, M.D.
Project manager:	Lisa Basham-Cruz

Keywords: NDA review, clinical studies, one-way analysis of variance, analysis of covariance, responder analysis

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Two studies were conducted to assess the immediate hypnotic effect and persistence in hypnotic effect of modified-release zolpidem formulation (zolpidem-MR) in adult and elderly patients (Study EFC4529 using zolpidem-MR 12.5 mg and Study EFC4530 using zolpidem-MR 6.25 mg, respectively) with primary insomnia.

I conclude that zolpidem-MR 12.5 mg and zolpidem-MR 6.25 mg are effective in providing *immediate* hypnotic effect during the first 8 hours after lights-out, by reducing the total wake time after sleep onset as measured by digital polysomnography (PSG). There is also strong evidence that zolpidem-MR improved sleep induction (measured by latency to persistent sleep), sleep duration (measured by sleep efficiency), and quality of sleep during Nights 1 and 2.

Although there is evidence that both zolpidem-MR 12.5 mg and zolpidem-MR 6.25 are effective in providing *persistence* in hypnotic effect, by reducing WASO during the first 6 hours after lights-out at Nights 15 and 16, this evidence is not conclusive to warrant a claim (See Section 1.3).

Analyses on next-day residual effects and rebound effects were conducted. There was no evidence of next-day residual effects, measured either objectively or subjectively. In terms of rebound effects, both studies observed rebound effects after the first night of abrupt discontinuation of zolpidem-MR 12.5 mg and of zolpidem-MR 6.25 mg. On the second night (N23), there appears to be no worsening on WASO, SE, and LPS compared with the results at baseline in the placebo, zolpidem-MR 12.5 and in the zolpidem-MR 6.25 group. However, the improvement on WASO, SE and LPS in both studies favored the placebo group.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

1.2.1 INTRODUCTION

Zolpidem is a non-benzodiazepine hypnotic, which possesses a specific affinity for the benzodiapine BZ_1 receptor subtype of the $GABA_A$ complex. Currently, the applicant, Sanofi-Synthelabo, is seeking FDA approval to market a modified-release formulation of zolpidem (zolpidem-MR). The principle of this formulation is to maintain the same elimination half-life, and to modify the release of zolpidem in order to maintain appropriate plasma concentrations during the middle of the night (3 to 6 hours) without increasing residual effects. A 2-layer coated tablet was developed which provides biphasic zolpidem release: immediate release followed by prolonged release.

The overall objective of the two studies was to demonstrate the hypnotic efficacy of zolpidem-MR (6.25 and 12.5 mg), and particularly that 12.5 mg or 6.25 mg of zolpidem-MR allowed sleep maintenance by reducing the total time awake after sleep onset, as compared with placebo, in both elderly and adult insomniac patients.

1.2.2 STUDY DESIGN

Two randomized, multi-center, double-blind, placebo-controlled studies of zolpidem-MR in patients with primary insomnia were conducted in the United States, Canada, Europe, and Australia. In the first study, EFC4529, adult patients (18 – 64 years of age) with primary insomnia were randomized to receive either 12.5 mg zolpidem-MR or placebo. Meanwhile in the second study, EFC4530, elderly patients (65 years of age and above) with primary insomnia were randomized to receive either 6.25 mg zolpidem-MR or placebo.

Both studies lasted approximately 30 days for each patient and consisted of the following periods:

1. a screening visit
2. a single-blind placebo run-in period (completed in the same week as the screening visit): two consecutive nights (SN1 and SN2) of polysomnography (PSG) screening in a sleep laboratory with single-blind placebo
3. a double-blind treatment period comprising
    a. two consecutive nights (N1 and N2) of PSG in a sleep laboratory with double-blind study treatment
    b. twelve nights of outpatient double-blind study treatment
    c. two consecutive nights (N15 and N16) of PSG in a sleep laboratory with double-blind study treatment
    d. five nights of outpatient double-blind study treatment
4. a single-blind placebo run-out period: two consecutive nights (N22 and N23) in a sleep laboratory with single-blind placebo.

1.2.3 STATISTICAL ANALYSIS

In both studies, the primary analysis was based on the intent-to-treat population taking into account all patients who were randomized, took at least one dose of double-blind study medication, and provided at least one post-baseline efficacy measurement. All statistical analyses were performed at the 0.05 global significance level using 2-sided tests based on a step-down procedure.

The primary efficacy measured in both studies was the mean change on the PSG WASO (wake time after sleep onset) calculated:

- For the immediate effect, as the mean of the first two treated nights N1 and N2 minus the mean of the two screening nights SN1 and SN2;
- For the persistence of effect, as the mean of the two treated nights N15 and N16 minus the mean of the two screening nights SN1 and SN2 using observed cases only.

In Study EFC4529, the efficacy variable, PSG WASO, was calculated based on the first 8 hours of the night. A one-way analysis of variance (ANOVA) was used to analyze the mean change on PSG WASO for the immediate effect. If the immediate effect was significant at the 0.05 level then another one-way ANOVA was used to analyze the mean change of PSG WASO for the persistence of effect at the 0.05 signifi cance level. An imbalance at baseline in PSG measurement was observed, and analysis of covariance (ANCOVA) adjusting for baseline PSG was added post hoc to the pre-specified analysis.

The main secondary endpoints were prioritized[1] in a step-down procedure, stopping as soon as N1/N2 for an endpoint was not statistically significant at the 0.05 level.

In Study EFC4530, slight modifications of the primary efficacy variable and of the primary and secondary analyses were made with the Agency's concurrence. The efficacy variable, PSG WASO was calculated based on the first 6 hours of the night, and the treatment groups were compared using analysis of covariance (ANCOVA) with baseline value as covariate in order to better take into account the baseline level in the analysis. A similar conditional procedure was applied for the immediate effect and the persistence of effect.

The main secondary endpoints were prioritized[1] in a step-down procedure and analyzed using a Bonferroni-Hommel procedure. This involved testing the primary endpoint first, and if either both N1/N2 and N15/N16 were significant at the 0.05 level, or one was significant at the 0.025 level, the first secondary endpoint was then tested. The same procedure was repeated for the subsequent secondary endpoints in the prioritized order.

The applicant also formulated several other endpoints for the study of residual effects and rebound effects and conducted additional analyses on the primary efficacy variable (e.g. subgroup analyses, subset analyses).

1.2.4 SPONSOR'S RESULTS AND CONCLUSIONS

The following summarizes some of the applicant's results and conclusions:

1. Both studies (EFC4529 and EFC 4530) confirmed the immediate hypnotic effect of zolpidem (6.25 mg and 12.5 mg) by reducing the WASO during the first 8 hours after lights-out in adult patients, and during the first 6 hours after lights-out in elderly patients.
2. Although sleep maintenance by reducing PSG WASO during the first 8 hours after lights-out at Nights 15 and 16 in adult patients taking zolpidem-MR 12.5 mg did not attain statistical significance in comparison with placebo (Study EFC4530), there was a noticeable difference between zolpidem-MR 12.5 mg and placebo in the reduction of PSG WASO during the first 6 hours after lights-out. This result was reflected in Study EFC4530 in which zolpidem-MR 6.25 mg was shown to maintain sleep by reducing the WASO during the first 6 hours after lights-out at Nights 15 and 16 in elderly patients with primary insomnia, in comparison with placebo.
3. Both studies showed that zolpidem-MR (6.25 mg and 12.5 mg) decreased sleep latency and increased sleep duration in comparison.
4. There is no evidence of next day residual effect observed in the zolpidem 6.25 mg or zolpidem 12.5 mg groups.
5. A rebound effect was observed on the first night after abrupt discontinuation in the zolpidem-MR 6.25 mg and 12.5 mg groups but not on the second night.
6. Zolpidem-MR 6.25 mg and 12.5 mg are well-tolerated.

[1] The main secondary prioritized endpoints are PSG sleep efficiency, PSG sleep latency to persistent sleep, and quality of sleep. Other secondary criteria are patient's global impression item 1, refreshing quality of sleep, subjective WASO, subjective total sleep time (TST), subjective sleep onset latency (SOL), PSG number of awakenings, subjective number of awakenings, difficulties in activities due to sleep problems.

1.3 STATISTICAL ISSUES AND FINDINGS

Several issues were identified after reviewing this NDA submission that influenced my conclusion, particularly on the efficacy of zolpidem-MR in providing *persistence* in hypnotic effect. Some issues were less crucial and can easily be addressed by post-hoc analyses (see Section 5.1). However, there are two vital issues that must be pondered upon before a decision could be made about the efficacy of zolpidem-MR in providing *persistence* in hypnotic effect at Nights 15 and 16, and they are:

1. How important is study replication?
2. How important is the quality of sleep in relation to effective hypnotic effect?

The biggest question that needs to be addressed is whether there is replication of persistence in effect. Although the sponsor was able to demonstrate efficacy at Nights 15 and 16 in both studies, by reducing WASO during the first 6 hours, technically, they were only able to achieve this, based on primary efficacy analysis in one study (EFC4530). In Study EFC4529, they did this analysis after the blind was broken.

In relation to number 1, secondary efficacy analyses using the appropriate statistical procedure and post-hoc analysis were conducted to assess the efficacy of zolpidem-MR in relation to other sleep variables (see Section 3.1.5 and Appendix A.1). True enough, effective reduction in PSG WASO during the first 8 hours at Nights 1 and 2 coincided with sleep efficiency, latency to persistent sleep, and better sleep quality among individuals taking zolpidem-MR over the placebo. However, this was not evident during Nights 15 and 16. If we were to believe that there is an effective reduction in PSG WASO during the first 6 hours at Nights 15 and 16 in both studies, then this should also be reflected in better quality of sleep among these individuals taking zolpidem-MR over the placebo. But post-hoc analyses (see Appendix A.1) show that there is a decrease in quality of sleep among these patients in the zolpidem-MR group or placebo group. This decrease in quality of sleep appeared to be correlated with increasing number of awakenings during the night among these individuals. Therefore, based on this new evidence, it is really debatable whether zolpidem-MR works at Night 15 and 16. Although there is reduction in PSG WASO during the first 6 hours at Nights 15 and 16, this evidence may not be conclusive enough to warrant a claim of efficacy.

As stated earlier, there were issues that I deemed less crucial, but nonetheless important. The following issues were either resolved or data were re-analyzed to address these problems in this review.

1. choice of primary efficacy analysis method in Study EFC4529
2. a stepdown procedure following a non-statistically significant finding at Nights 15 and 16 in Study EFC4529
3. handling of missing data due to drop-outs
4. inclusion of subjects in the analysis identified to have major protocol deviation.

A summary of these issues can be found in Section 5.1.

2 INTRODUCTION

2.1 OVERVIEW

This is a review of the clinical data in adult (aged 18 to 65 years) and elderly (aged 65 years and over) patients with primary insomnia treated with zolpidem-MR (12.5 mg and 6.25 mg).

According to the applicant's description, zolpidem is a non-benzodiazepine hypnotic, which possesses a specific affinity for the benzodiapine BZ_1 receptor subtype of the $GABA_A$ complex.

Currently, the applicant, Sanofi-Synthelabo, is seeking FDA approval to market a modified-release (MR) formulation of zolpidem. According to the applicant, the principle of this formulation is to maintain the same elimination half-life, and to modify the release of zolpidem in order to maintain appropriate plasma concentrations during the middle of the night (3 to 6 hours) without increasing residual effects. A 2-layer coated tablet was developed which the applicant claims would provide biphasic zolpidem release: immediate release followed by prolonged release.

The overall objective of the two studies was to demonstrate the hypnotic efficacy of zolpidem-MR (6.25 and 12.5 mg), and particularly that 12.5 mg or 6.25 mg of zolpidem-MR allowed sleep maintenance by reducing the total time awake after sleep onset, as compared with placebo, in both elderly and adult insomniac patients.

This statistical review focuses on the two clinical studies conducted in patients with primary insomnia:

1. Study EFC4529, an international, multi-center, randomized, double-blind, placebo-controlled study in two parallel groups (12.5 mg zolpidem and placebo), using polysomnography (PSG) and subjective assessments in adult patients (aged 18 to 65 years) with primary insomnia, and
2. Study EFC4530, an international, multi-center, randomized, double-blind, placebo-controlled study in two parallel groups (6.25 mg zolpidem and placebo), using polysomnography (PSG) and subjective assessments in elderly patients (aged 65 years and over) with primary insomnia.

2.2 DATA SOURCES

This statistical review is based on data submitted in Studies EFC4529 and EFC4530.

The electronic submission of this NDA can be found on the internal network drive at \\Cdsesub1\n21774\N_000\2004-06-08 .

The clinical study report for Studies EFC4529 and EFC4530 is located at \\Cdsesub1\n21774\N_000\2004-06-08\clinstat .

The electronic datasets for all the studies are under \\Cdsesub1\n21774\N_000\2004-06-08\crt\datasets .

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

This statistical review focuses on the two clinical studies (EFC4529 and EFC4530) in patients with primary insomnia. Study EFC4529 enrolled adult patients (aged 18 to 65 years) with primary insomnia, and these patients were randomized to receive either zolpidem-MR 12.5 mg or placebo. On the other hand, study EFC4530 enrolled elderly patients (aged 65 years and over) with primary insomnia, and these patients were randomized to receive either zolpidem-MR 6.25 mg or placebo.

3.1.1 STUDY DESIGN

Both studies, EFC4529 and EFC4530, were randomized, multicenter, double-blind, placebo-controlled studies of zolpidem-MR in patients with primary insomnia. Study EFC4529 was conducted in the United States, Canada and Australia, while study EFC4530 was conducted in Argentina, Canada, Mexico, France, Germany and United States. Both studies lasted approximately 30 days for each patient and consisted of the following periods:

1. a screening visit
2. a single-blind placebo run-in period (completed in the same week as the screening visit): two consecutive nights (SN1 and SN2) of polysomnography (PSG) screening in a sleep laboratory with single-blind placebo
3. a double-blind treatment period that included
    a. two consecutive nights (N1 and N2) of PSG in a sleep laboratory with double-blind study treatment
    b. twelve nights of outpatient double-blind study treatment
    c. two consecutive nights (N15 and N16) of PSG in a sleep laboratory with double-blind study treatment
    d. five nights of outpatient double-blind study treatment
4. a single-blind placebo run-out period: two consecutive nights (N22 and N23) in a sleep laboratory with single-blind placebo.

3.1.2 STUDY OBJECTIVES

The primary objective of the two studies was to evaluate the hypnotic efficacy of 12.5 mg (EFC4529) and 6.25 mg (EFC4530) of zolpidem-MR compared to placebo, using polysomnography (PSG) and subjective sleep questionnaire. The secondary objectives of these studies were to evaluate the residual effects (objectively by psychometric tests, or subjectively by patient's morning questionnaire) that may be associated with zolpidem-MR as compared with placebo, to compare the effect on sleep following abrupt discontinuation between zolpidem-MR and placebo after 21 nights of treatment, to evaluate the clinical safety and tolerability of zolpidem-MR compared with placebo, and to assess the residual plasma concentrations of zolpidem-MR.

3.1.3 EFFICACY PARAMETERS AND STATISTICAL ANALYSIS PLAN

The primary efficacy variable was the mean change on WASO (during 1 to 8 hours for EFC4529 and during 1 to 6 hours for EFC4530) measured by PSG recordings. Both efficacy variables were calculated for the immediate effect (i.e. on the mean of the first 2 treated nights minus the mean of the 2 screening nights) and for the persistence of effect (i.e. on the mean of the 2 treated nights N15 and N16 minus the mean of the 2 screening nights).

In both studies, the primary analysis was based on the intent-to-treat population taking into account all patients who were randomized, took at least one dose of double-blind study medication, and provided at least one post-baseline efficacy measurement. All statistical analyses were performed at the 0.05 global significance level using 2-sided tests.

In Study EFC4529, a one-way analysis of variance (ANOVA) was used to analyze the mean change on PSG WASO for the immediate effect. If the immediate effect was significant at the 0.05 level then another one-way ANOVA was used to analyze the mean change of PSG WASO for the persistence of effect at the 0.05 significance level using observed cases only (i.e. subjects who had missing PSG recordings at nights 15 and 16 were excluded from the second analysis). An imbalance at baseline in PSG measurement was observed, and analysis of covariance (ANCOVA) adjusting for baseline PSG was added post hoc to the pre-specified analysis. Meanwhile, the main secondary endpoints were prioritized[2] in a step-down procedure using one-way ANOVA, except on PGI, stopping as soon as N1/N2 for an endpoint was not statistically significant at the 0.05 level.

In Study EFC4530, slight modifications of the primary efficacy variable and the primary and secondary analyses were made with the Agency's concurrence. The efficacy variable, PSG WASO was calculated based on the first 6 hours of the night, and the treatment groups were compared using analysis of covariance (ANCOVA) with baseline value as covariate in order to better take the baseline level into account in the analysis. A similar conditional procedure and method of handling of missing data were applied for the immediate effect and the persistence of effect. Furthermore, the main secondary endpoints were also prioritized[1] in a step-down procedure and analyzed using a Bonferroni-Hommel procedure. This involved testing the primary endpoint first, and if either both N1/N2 and N15/N16 were significant at the 0.05 level, or one was significant at the 0.025 level, the first secondary endpoint was then tested. The same procedure was repeated for the subsequent secondary endpoints in the prioritized order.

A variety of endpoints for the study of residual effects and rebound effects were assessed as part of this statistical review. The parameters for the residual effects include the Digit Symbol Substitution test (DSS), the Rey auditory verbal learning test (RAVLT), and two questions on the morning questionnaire. Parameters for the rebound effects include the WASO, sleep efficiency (SE) and latency to persistent sleep (LPS) on Nights 22 and 23. Additional analyses on the primary efficacy variable were also conducted (e.g. subgroup analyses, subset analyses) to support the efficacy claim.

[2] Secondary prioritized endpoints: PSG sleep efficiency, PSG sleep latency to persistent sleep, quality of sleep, patient's global impression item 1, refreshing quality of sleep, subjective WASO, subjective total sleep time (TST), subjective sleep onset latency (SOL), PSG number of awakenings, subjective number of awakenings, difficulties in activities due to sleep problems.

3.1.4 SUMMARY OF RESULTS (DIRECTLY TAKEN FROM THE APPLICANT'S SUMMARY OF EFFICACY AND PART OF SAFETY)

STUDY EFC4529

The adjusted mean total PSG WASO (1 to 8 hours) from the ANCOVA analysis improved from baseline significantly more in the zolpidem-MR 12.5 mg group than in the placebo group (40:25 versus 14:56 minutes: seconds; $p<0.0001$) on nights 1 and 2 (N1/N2), but the treatment difference was no longer significant on nights 15 and 16 (25:23 versus 18:17 min:sec for zolpidem-MR 12.5 and placebo, respectively) .

The by-hour ANCOVA analysis of the effect of the study treatments on PSG WASO showed that the improvement was greater in the zolpidem-MR 12.5 mg group than in the placebo group up to Hour 7 on N1/N2, and from Hour 2 to Hour 5 on N15/N16. Furthermore, ANCOVA analysis of the effect of the study treatments on PSG WASO during the first 6 hours after lights-out demonstrated a considerable improvement in the zolpidem-MR 12.5 mg group than in the placebo group on N1/N2 (33:49 versus 10:24 min:sec) and (30:12 versus 13:43 min:sec) on N15/N16.

Additional analyses on the immediate hypnotic effect on N1/N2 showed that, compared to placebo, zolpidem-MR 12.5 mg increased the sleep duration (measured subjectively by total sleep time and objectively by PSG sleep efficiency), decreased the sleep latency (measured subjectively by sleep onset latency and objectively by PSG latency to persistent sleep), reduced the number of awakenings (measured both objectively and subjectively), decreased subjective WASO, and improved the quality of sleep, the patient's global impression (using item 1) and the refreshing quality of sleep.

On the other hand, additional analyses on the persistence of hypnotic effect on N15/N16 revealed that zolpidem-MR 12.5 was superior to placebo in terms of sleep efficiency, latency to persistent sleep and number of awakenings, all measured objectively, and on patient's global impression (using item 1) and subjective number of awakenings.

These results imply the hypnotic effect of zolpidem-MR 12.5 and suggest that zolpidem-MR 12.5 is effective in sleep maintenance by reducing the WASO during the first 6 hours after lights-out in adult patients with primary insomnia.

The objective assessment of next day residual effects by psychometric tests revealed no significant decrease in performance with zolpidem-MR 12.5 mg. The subjective assessment on patient questionnaires showed no evidence of next day residual effects on Days 1 and 2 or on Days 15 and 16.

A rebound effect (worsening compared with baseline) was observed after the first night of abrupt discontinuation of zolpidem-MR 12.5 mg for WASO, sleep efficiency, and latency to persistent sleep (measured objectively), but not on the second night.

STUDY EFC4530

This study demonstrated the effectiveness of zolpidem-MR 6.25 mg on sleep maintenance by reducing the WASO during the first 6 hours after lights-out in adult patients with primary insomnia,

as measured objectively by PSG. The adjusted mean total PSG WASO (1 to 6 hours) from the ANCOVA analysis improved from baseline significantly more in the zolpidem-MR 6.25 mg group than in the placebo group (32:41 versus 6:59 minutes:seconds; $p<0.0001$) on nights 1 and 2 (N1/N2), and on nights 15 and 16 (18:22 versus 6:56 min:sec, $p=0.0042$, for zolpidem-MR 6.25 mg and placebo, respectively).

The by-hour ANCOVA analysis of the effect of the study treatments on PSG WASO demonstrated that the improvement was greater in the zolpidem-MR 6.25 mg group than in the placebo group from Hour 2 up to Hour 6 on N1/N2, and up to Hour 4 on N15/N16.

Additional analyses on the immediate hypnotic effect on N1/N2 showed that, compared to placebo, zolpidem-MR 6.25 mg increased the sleep duration (measured subjectively by total sleep time and objectively by PSG sleep efficiency), decreased the sleep latency (measured objectively by PSG latency to persistent sleep), decreased subjective WASO, and improved the quality of sleep, the patient's global impression (using item 1) and the refreshing quality of sleep.

Additional analyses on the persistence of hypnotic effect on N15/N16 revealed that zolpidem-MR 6.25 mg was superior to placebo in terms of latency to persistent sleep measured objectively, on patient's global impression (using item 1). It also shows slightly favorable results on sleep efficiency measured objectively in zolpidem-MR 6.25 mg compared to placebo.

The objective assessment of next day residual effects by psychometric tests revealed no significant decrease in performance with zolpidem-MR 6.25 mg. The subjective assessment on patient questionnaires showed no evidence of next day residual effects on Days 1 and 2, or on Days 15 and 16.

A rebound effect (worsening compared with baseline) was observed after the first night of abrupt discontinuation of zolpidem-MR 6.25 mg for WASO, sleep efficiency, and latency to persistent sleep (measured objectively), but not on the second night.

3.1.5 DETAILED REVIEW OF STUDIES EFC4529 AND EFC4530

EFC4529

Study EFC4529 was a randomized, double-blind, multicenter, placebo-controlled study to demonstrate the immediate hypnotic efficacy and the persistence of hypnotic efficacy of zolpidem-MR 12.5 mg, by reducing the total time awake after sleep onset, as compared to placebo, in adult insomniac patients. The study lasted approximately 30 days for each patient, including a screening visit, a single-blind placebo run-in period, a three-week double-blind treatment period that included two consecutive nights (N1 and N2) of PSG in a sleep laboratory, 12 nights of outpatient treatments, two consecutive nights (N15 and N16) of PSG in a sleep laboratory, five more nights of outpatient treatments, and lastly, a single-blind placebo run-out period.

A sample size of 100 patients per group was considered to be sufficient to detect a treatment difference (versus a placebo) in PSG WASO of 20 minutes (SD = 45 minutes) with power at least 80%, a type-I error probability of 5% and a 2-sided comparison. This sample size of 100 patients per

group takes into account a maximum of 4% possible missing data and 10% non-available data due to possible drop-outs (for the analysis on N15 and N16). The standard deviation (SD) was estimated based on a subgroup of patients included in previous study (NDA-LSH17) with PSG WASO at least 40 minutes on the mean of the two baseline nights. A 20-minute difference between treatment groups for PSG WASO was considered to be clinically meaningful.

A total of 545 patients were screened in the study of whom 333 were not randomized. The main reason for screen failure was "inclusion or exclusion not respected" in 272 out of 333 patients (82%). Of the 212 patients randomized to the study, 110 were randomized to the placebo group, and 102 were randomized to the zolpidem-MR 12.5 mg group (Table 2). Patients were recruited from 40 centers (6 in Australia, 5 in Canada, and 29 in the United States).

Out of 212 patients, 20 patients (9%) withdrew from the study: 11/110 (10%) in the placebo group, and 9/102 (9%) in the zolpidem-MR 12.5 mg group. The most frequent specified reason for premature withdrawal was adverse event [2 (2%) in the placebo and 6 (6%) in the zolpidem-MR 12.5 mg group]. Furthermore, 48 patients (27 in the placebo and 21 in the zolpidem-MR 12.5 mg group) were not included in the PP population. The main deviation was the non-respect of the inclusion/exclusion criteria.

Table 1: Disposition of Patients

	Total	Active	Placebo
Screened	545		
Non-randomized Patients	333 (61%)		
Inclusion/exclusion criteria not respected	272 (82%)		
Adverse event	3 (1%)		
Withdrawal of consent	21 (6%)		
Lost to follow-up	4 (4%)		
Other	23 (7%)		
Exposed Population	212	102	110
Randomized (Intent-to-Treat)	212	102	110
Completed	192 (91%)	93 (91%)	99 (90%)
Discontinued	20 (9%)	9 (9%)	11 (10%)
Disease progression/lack of efficacy	1	0	1
Adverse event	8	6	2
Poor compliance to protocol	1	0	1
Investigator/subject's request	4	0	4
Subject's loss to follow-up	1	0	1
Other reason	5	3	2
ITT population excluding major deviations[1]	182	93	89
Per Protocol Population	164	81	83

[1] Major deviations include mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours (27 patients), and study site not in compliance with GCP (4 patients)

The majority (58%) of the exposed population was female. The mean age (±SD) for the combined study groups was 44 ± 13 years, ranging from 18 to 64 years of age. The demographic characteristics (e.g. race, age, BMI) of patients who participated in this study were comparable between the treatment groups. The mean duration of the current episode of insomnia was 103 ± 105 months in

the placebo group, and 112 ± 135 months in the zolpidem-MR 12.5 mg group. At baseline, patients had a mean WASO of 87:37 ± 40:53 min:sec, a mean total sleep time (TST) of 354:42 ± 49:43 min:sec, a mean latency to persistent sleep (LPS) of 42:46 ± 34:46 min:sec, and a mean number of nocturnal awakenings of 10 ± 4 for the combined study groups. Other baseline characteristics are summarized in Table 2.

Table 2: Summary of Patient's PSG Results and Sleep Morning Questionnaire at Screening - Exposed Population

		Placebo (N=110)	Zolpidem-MR 12.5 mg (N=102)	Total (N=212)
TST (min:sec)	n	110	102	212
	Median	356:45	370:30	362:00
	Mean (SD)	348:05 (54:15)	361:50 (43:28)	354:42 (49:43)
	Min - Max	136:15 - 455:30	239:45 - 445:15	136:15 - 455:30
Total WASO (min:sec)	n	110	102	212
	Median	88:08	81:15	82:53
	Mean (SD)	93:19 (44:55)	81:28 (35:13)	87:37 (40:53)
	Min - Max	19:00 - 247:15	8:30 - 209:15	8:30 - 247:15
WASO H1 to H3 (min:sec)	n	110	102	212
	Median	14:15	14:08	14:08
	Mean (SD)	21:01 (18:59)	15:51 (13:43)	18:32 (16:49)
	Min - Max	0:00 - 106:30	0:00 - 75:00	0:00 - 106:30
WASO H4 to H6 (min:sec)	n	110	102	212
	Median	33:23	25:38	30:08
	Mean (SD)	38:13 (26:16)	32:33 (22:00)	35:29 (24:25)
	Min - Max	2:30 - 133:00	2:45 - 105:00	2:30 - 133:00
LPS (min:sec)	n	110	102	212
	Median	33:38	33:15	33:23
	Mean (SD)	43:47 (36:47)	41:41 (32:36)	42:46 (34:46)
	Min - Max	2:00 - 192:30	3:00 - 211:30	2:00 - 211:30
Number of awakenings	n	110	102	212
	Median	10	9	10
	Mean (SD)	10.2 (4.2)	9.2 (4.1)	9.7 (4.2)
	Min - Max	3 - 25	2 - 22	2 – 25

		Placebo (N=110)	Zolpidem-MR 12.5 mg (N=102)	Total (N=212)
Duration of sleep (min:sec)	n	109	102	211
	Median	330:00	315:00	330:00
	Mean (SD)	321:52 (77:07)	322:58 (67:14)	322:24 (72:20)
	Min - Max	75:00 - 495:00	150:00 - 540:00	75:00 - 540:00
Time spent awake after falling asleep (min:sec)	n	109	101	210
	Median	60:00	65:00	61:15
	Mean (SD)	81:13 (62:28)	81:29 (56:45)	81:20 (59:39)
	Min - Max	7:30 - 375:00	0:00 - 240:00	0:00 - 375:00
Sleep onset latency (min:sec)	n	110	102	212
	Median	51:15	52:30	52:30
	Mean (SD)	61:57 (55:12)	61:24 (41:42)	61:41 (49:03)
	Min - Max	7:30 - 480:00	5:00 - 210:00	5:00 - 480:00
Number of awakenings	n	110	102	212
	Median	4	4	4
	Mean (SD)	5.1 (5.4)	4.9 (3.3)	5.0 (4.5)
	Min - Max	1 - 45	1 - 23	1 – 45

[ref='PGM= SL80075023.EFC4529.CSR.BS\PGM_RPT.t106demo.sas. OUT= OUTPUT\t106demo_4.ged (25NOV2003 - 13:53)

Source: CRS-BDY-EFC4529-EN-E01 page 50/136

Table 3 summarizes the results from the primary efficacy analysis. As stated in the analysis plan, one-way ANOVA is the analysis method for both primary outcome and secondary outcome variables. On N1/N2, the mean total WASO decreased (improved) from baseline (screening) by 17:42 ± 41:59 and 37:25 ± 33:16 min:sec in the placebo and zolpidem-MR 12.5 mg groups, respectively based on the ITT population. The difference between treatment groups using ANOVA analysis was statistically significant (p=0.0002). On N15/N16, the mean total WASO decreased (improved) from baseline by 20:25 ± 43:01 and 23:05 ± 39:27 min:sec in the placebo and zolpidem-MR 12.5 groups, respectively based on the ITT population. However, the difference between treatment groups was not statistically significant using ANOVA analysis. These results were consistent when ANCOVA was used and when major deviations were excluded in the ITT population. Major deviations are mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours (27 patients), and study site not in compliance with GCP (4 patients).

Table 3: Results on the Comparison of the PSG WASO data, Zolpidem-MR 12.5 mg versus Placebo

	N	Placebo	Active	Mean Diff	95% CI	p-value
ITT POPULATION						
Completed WASO (ANOVA)						
Nights 1, 2	212	-17:42	-37:25	-19:44	(-30:02, -9:25)	0.0002
Nights 15, 16	199	-20:25	-23:05	-2:40	(-14:14, 8:53)	0.6489
Completed WASO (ANCOVA)						
Nights 1, 2	212	-14:56	-40:25	-25:29	(-34:25, -16:33)	<0.0001
Nights 15, 16	199	-18:17	-25:23	-7:06	(-17:47, 3:35)	0.1913
ITT Population excluding major deviations[1]						
Completed WASO (ANOVA)						
Nights 1, 2	182	-19:16	-40:54	-21:38		0.0002
Nights 15, 16	170	-22:51	-25:17	-2:26		0.7064
Completed WASO (ANCOVA)						
Nights 1, 2	182	-14:54	-45:05	-30:11		<0.0001
Nights 15, 16	170	-19:35	-28:23	-8:48		0.1542

[1] Major deviations include mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours (27 patients), and study site not in compliance with GCP (4 patients)

Supportive efficacy analyses were conducted by the applicant (post-hoc) in order to better define the effects of the study treatment on WASO. This includes per-hour analyses of PSG WASO, as well as analyses on different parts of the nights divided into three parts (first 3 hours, middle 3 hours, and last 2 hours) using ANCOVA adjusting for baseline PSG WASO. The applicant also conducted analysis on the effect of zolpidem-MR 12.5 mg on WASO during the first 6 hours using ANCOVA adjusting for baseline PSG WASO. The results are summarized in Tables 4 to 5. The results provided showed apparent improvements in mean PSG WASO from baseline on Nights 1 and 2 across different hours/parts of the nights, and in mean PSG WASO from baseline on Nights 15 and 16 at least up to Hour 6. Accounting for multiplicity, there still appeared to be a statistical difference between treatment groups on Nights 1 and 2 at Hours 2 to 5, and on Nights 15 and 16 at Hours 2 to 5 as well (Table 5). The

results between using the ITT population and the exclusion of major deviations from the ITT population did not differ except on the last 2 hours of WASO (H7 & H8).

Table 4: Results of the ANCOVA for the PSG WASO during Parts of the Night

	N	Placebo	Active	Mean Diff	95% CI	p-value
ITT POPULATION						
WASO H1 to H3						
Nights 1, 2	212	-4:35	-12:48	-8:13	(-10:53, -5:32)	<0.0001
Nights 15, 16	199	-3:47	-11:42	-7:55	(-10:53, -4:57)	<0.0001
WASO H4 to H6						
Nights 1, 2	212	-5:36	-21:16	-15:40	(-21:28, -9:53)	<0.0001
Nights 15, 16	199	-9:31	-18:57	-9:26	(-15:15, -3:37)	0.0016
WASO H7 to H8						
Nights 1, 2	212	-3:29	-7:55	-4:26	(-9:54, 1:01)	0.1105
Nights 15, 16	199	-3:33	3:33	7:06	(0:05, 14:06)	0.0471
WASO H1 to H6						
Nights 1, 2	212	-10:24	-33:49	-23:25	(-30:14, -16:36)	<0.0001
Nights 15, 16	199	-13:43	-30:12	-16:29	(-23:46, -9:12)	<0.0001
ITT Population excluding major deviations**						
WASO H1 to H3						
Nights 1, 2	182	-4:40	-13:59	-9:19		<0.0001
Nights 15, 16	170	-3:57	-12:49	-8:52		<0.0001
WASO H4 to H6						
Nights 1, 2	182	-4:36	-22:46	-18:10		<0.0001
Nights 15, 16	170	-9:23	-20:14	-10:51		0.0011
WASO H7 to H8						
Nights 1, 2	182	-3:41	-10:24	-6:43		0.0276
Nights 15, 16	170	-4:13	2:38	6:51		0.0836
WASO H1 to H6						
Nights 1, 2	182	-9:23	-36:38	-27:15		<0.0001
Nights 15, 16	170	-13:40	-32:45	-19:05		<0.0001

*First part implies first three hours (H1+H2+H3)
** Major deviations include mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours (27 patients), and study site not in compliance with GCP (4 patients)

Table 5: Results of the ANCOVA of the comparison of the PSG WASO per hour data, Zolpidem-MR 12.5mg versus Placebo - ITT Population

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1/Nights 1, 2	212	0:01	-0:45	-0:46	[-1:32 ;-0:00]	(1,209)	0.0488 *
WASO H1/Nights 15, 16	199	0:22	-0:20	-0:42	[-1:31 ; 0:08]	(1,196)	0.1002
WASO H2/Nights 1, 2	212	-1:59	-5:42	-3:43	[-5:06 ;-2:20]	(1,209)	<0.0001 *
WASO H2/Nights 15, 16	199	-1:36	-4:51	-3:15	[-4:48 ;-1:41]	(1,196)	<0.0001 *
WASO H3/Nights 1, 2	212	-2:26	-6:34	-4:09	[-5:49 ;-2:29]	(1,209)	<0.0001 *
WASO H3/Nights 15, 16	199	-2:37	-6:46	-4:09	[-5:50 ;-2:27]	(1,195)	<0.0001 *
WASO H4/Nights 1, 2	212	-1:55	-7:46	-5:51	[-7:53 ;-3:49]	(1,208)	<0.0001 *
WASO H4/Nights 15, 16	199	-2:57	-8:08	-5:10	[-7:17 ;-3:04]	(1,196)	<0.0001 *
WASO H5/Nights 1, 2	212	-0:54	-7:26	-6:32	[-9:12 ;-3:51]	(1,209)	<0.0001 *
WASO H5/Nights 15, 16	199	-2:07	-7:12	-5:05	[-7:47 ;-2:23]	(1,196)	0.0003 *
WASO H6/Nights 1, 2	212	-2:35	-6:24	-3:49	[-6:40 ;-0:58]	(1,209)	0.0089 *
WASO H6/Nights 15, 16	199	-3:51	-3:42	0:10	[-2:44 ; 3:03]	(1,195)	0.9132
WASO H7/Nights 1, 2	212	-1:11	-4:07	-2:56	[-5:45 ;-0:08]	(1,209)	0.0405 *
WASO H7/Nights 15, 16	199	-1:56	0:56	2:52	[-0:40 ; 6:24]	(1,196)	0.1103
WASO H8/Nights 1, 2	212	-2:16	-3:50	-1:34	[-5:15 ; 2:08]	(1,209)	0.4054
WASO H8/Nights 15, 16	199	-1:37	2:36	4:14	[-0:16 ; 8:44]	(1,196)	0.0653

<ref>PGM= SL80075023.EFC4529.CSR.BS.PGM_RPT.t1111psg.sas OUT= OUTPUT.t1111psg_6.ged (25NOV2003 - 17:09)

*: p<0.05

Re-analyses of secondary outcomes using one-way ANOVA are presented in Table 6 in the order of priority. Using ITT population on N1/N2, the mean SE, and the mean LPS improved from baseline in both treatment groups, favoring the zolpidem-MR 12.5 mg group (i.e. mean difference in SE= 0.06, mean difference in LPS = -8:41). Meanwhile, the mean quality of sleep on Days 1 and 2 improved favoring the zolpidem-MR 12.5 treated group with mean difference = 0.7. Similar conclusion is reached when subjects who had major protocol deviations (defined as include mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours, and study site not in compliance with GCP) were excluded in the ITT population.

Using the ITT population on N15/N16, the mean SE, mean LPS, and the mean quality of sleep also showed some improvement from baseline in both treatment groups but these improvements were comparable in both treatment groups. It was not clear from the analysis section of the report how the applicant planned to proceed if secondary outcomes from N15/N16 were not statistically significant and the secondary outcome from N1/N2 was barely significant (p>0.025). To use the rule from Study EFC4530, the secondary analysis would be stopped after PSG latency to persistent sleep when the ITT population is used (Table 6).

When subjects who had major protocol deviations were excluded from the ITT population, there is evidence that latency to persistent sleep was different between the zolpidem-MR treated group and the placebo group during Nights 15 and 16, favoring the zolpidem-MR group (Table 6). Following the step-down procedure in Study EFC4530, it appeared that the patient global impression (PGI) score and the subjective and objective number of awakenings significantly favored the zolpidem-MR treated groups (Table 8).

Table 6: Results of the ANOVA of the comparison of the Secondary Outcome Variables, Zolpidem-MR 12.5mg versus Placebo

	N	Placebo	Active	p-value
ITT POPULATION				
PSG Sleep Efficiency (SE)				
Nights 1, 2	212	0.06	0.12	0.0002
Nights 15, 16	199	0.07	0.09	0.4401
PSG Latency to Persistent Sleep (LPS)				
Nights 1, 2	212	-14:14	-23:01	0.0411
Nights 15, 16	199	-14:44	-20:19	0.2704
Quality of Sleep (ANOVA)				
Days 1, 2	211	-0.3	-1.0	<0.0001
Days 15, 16	198	-0.4	-0.5	0.2150
ITT Population excluding major deviations[1]				
PSG Sleep Efficiency (SE)				
Nights 1, 2	182	0.06	0.13	<0.0001
Nights 15, 16	170	0.07	0.09	0.0885
PSG Latency to Persistent Sleep (LPS)				
Nights 1, 2	182	-8:47	-23:39	0.0003
Nights 15, 16	170	-8:55	-21:59	0.0096
Quality of Sleep (ANOVA)				
Days 1, 2	181	-0.32	-0.99	<0.0001
Days 15, 16	169	-0.40	-0.50	0.4211

[1] Major deviations include mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours (27 patients), and study site not in compliance with GCP (4 patients)

Table 7: Results of the ANOVA of the comparison of Other Secondary Outcome Variables, Zolpidem-MR 12.5mg versus Placebo - ITT Population

	N	Placebo	Active	p-value
Patient Global Impression (%)				
Day 2	201	52.0	74.7	0.0008
Day 15	199	36.9	85.3	<0.0001
Refreshing Quality of Sleep				
Days 1, 2	212	-0.3	-0.7	<0.0001
Days 15, 16	199	-0.4	-0.5	0.3356
Subjective Wake time after sleep (WASO)				
Days 1, 2	210	-7:46	-35:49	0.0006
Days 15, 16	196	-12:47	-23:26	0.2427
Subjective Total Sleep Time (TST)				
Days 1, 2	211	27:51	67:43	<0.0001
Days 15, 16	198	41:40	54:39	0.2301
Subjective Sleep Onset Latency (SOL)				
Days 1, 2	212	-11:23	-29:40	0.0024
Days 15, 16	197	-18:36	-28:04	0.1344
PSG Number of Awakenings				
Nights 1, 2	212	-1.0	-2.8	<0.0001
Nights 15, 16	199	-1.0	-2.6	0.0010
Subjective Number of Awakenings				
Days 1, 2	212	-1.0	-2.7	0.0001
Days 15, 16	197	-1.1	-2.2	0.0298
Disturbances in daily activities				
Nights 1, 2	212	-0.2	-0.3	0.0790
Nights 15, 16	199	-0.3	-0.6	0.0706

Table 8: Results of the ANOVA of the comparison of Other Secondary Outcome Variables, Zolpidem-MR 12.5mg versus Placebo - ITT Population with NO MAJOR DEVIATIONS

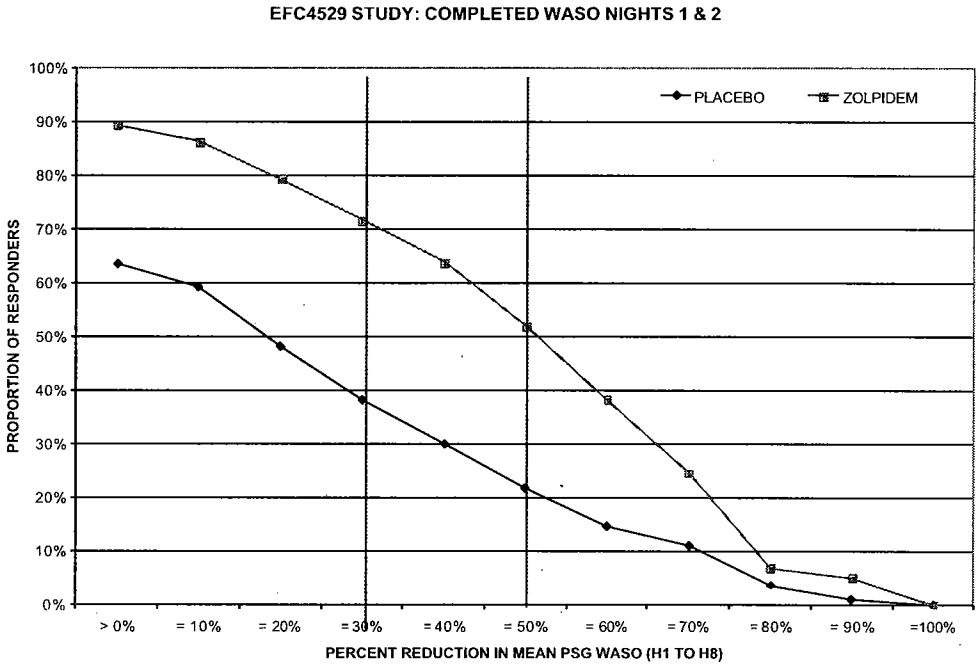
	N	Placebo	Active	p-value
Patient Global Impression (%)				
Day 2	173	54.2	77.8	0.0010
Day 15	170	38.6	82.8	<0.0001
Refreshing Quality of Sleep				
Days 1, 2	182	-0.3	-0.7	0.0001
Days 15, 16	170	-0.4	-0.5	0.3057
Subjective Wake time after sleep (WASO)				
Days 1, 2	180	-11:27	-38:51	0.0026
Days 15, 16	167	-16:14	-23:44	0.4701
Subjective Total Sleep Time (TST)				
Days 1, 2	181	34:35	69:16	0.0011
Days 15, 16	169	47:49	54:10	0.5938
Subjective Sleep Onset Latency (SOL)				
Days 1, 2	182	-6:00	-29:50	<0.0001
Days 15, 16	168	-15:31	-28:44	0.0398
PSG Number of Awakenings				
Nights 1, 2	182	-1.2	-2.9	0.0005
Nights 15, 16	170	-1.0	-2.7	0.0012
Subjective Number of Awakenings				
Days 1, 2	182	-0.8	-2.8	<0.0001
Days 15, 16	168	-1.2	-2.3	0.0127
Disturbances in daily activities				
Nights 1, 2	182	-0.1	-0.4	0.0446
Nights 15, 16	170	-0.4	-0.6	0.1922

I also carried out responder analysis to assess the sensitivity of the Observed Cases analysis performed by the sponsor in handling missing data. The responder analysis is based on percent decrease in mean pain score from baseline. The percent decrease was classified in 10-percent increments (e.g. =10%, =20%,..., =100% pain reduction) giving cumulative distribution functions of pain reduction by treatment groups. In this analysis, patients who withdrew from the study before Night 15, regardless of the reason for withdrawal, were classified as non-responders at N15/N16.

The proportions of responders based on PSG WASO recording during the first 8 hours and during the first 6 hours at Nights 1 and 2, and Nights 15 and 16, for all the various definitions of responder considered are presented (Figures 1 – 4). Inspection of these graphs suggests that there are apparent differences in the proportion of responders between the two treatment groups during the first 8 hours and during the first 6 hours at Nights 1 and 2, favoring zolpidem-MR 12.5 mg group. Although there are differences in the proportion of responders between the treatment groups during the first 8 hours at Nights 15 and 16, these differences became more pronounced when PSG WASO

during the first 6 hours was plotted. Overall, higher proportions of subjects in the zolpidem-MR 12.5 mg group were treatment responders compared to the placebo-treated group when different definitions of responder (based on different percent pain reduction) were used. These results were consistent with the Observed Cases Analyses. Furthermore, removing subjects with major deviations did not affect the findings (i.e. response profile) either at Nights 1 & 2 or Nights 15 & 16 using completed WASO or WASO H1 to H6 (Figures 5 – 8).

Figure 1: Response Profile at Nights 1 and 2 using PSG WASO during the first 8 hours after lights-out - ITT Population



APPEARS THIS WAY
ON ORIGINAL

Figure 2: Response Profile at Nights 1 and 2 using PSG WASO during the first6 hours after lights-out - ITT Population

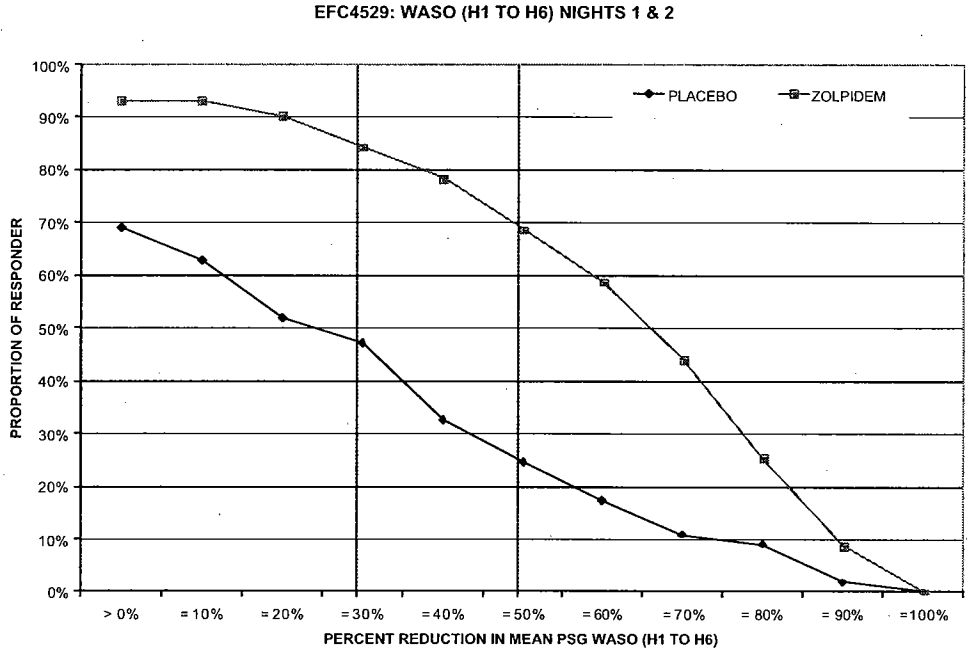


Figure 3: Response Profile at Nights 15 and 16 using PSG WASO during the first 8 hours after lights-out - ITT Population

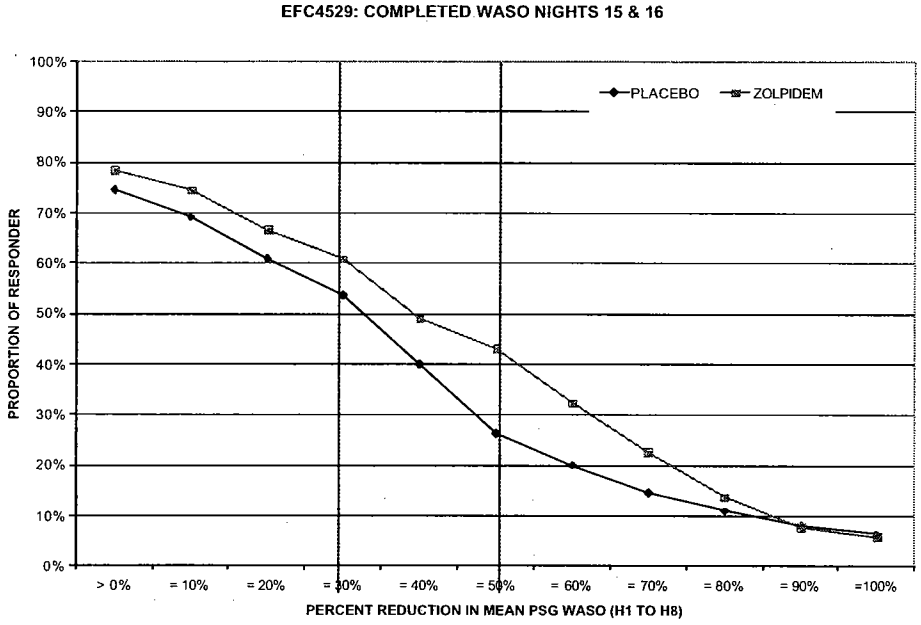


Figure 4: Response Profile at Nights 15 and 16 using PSG WASO during the first 6 hours after lights-out - ITT Population

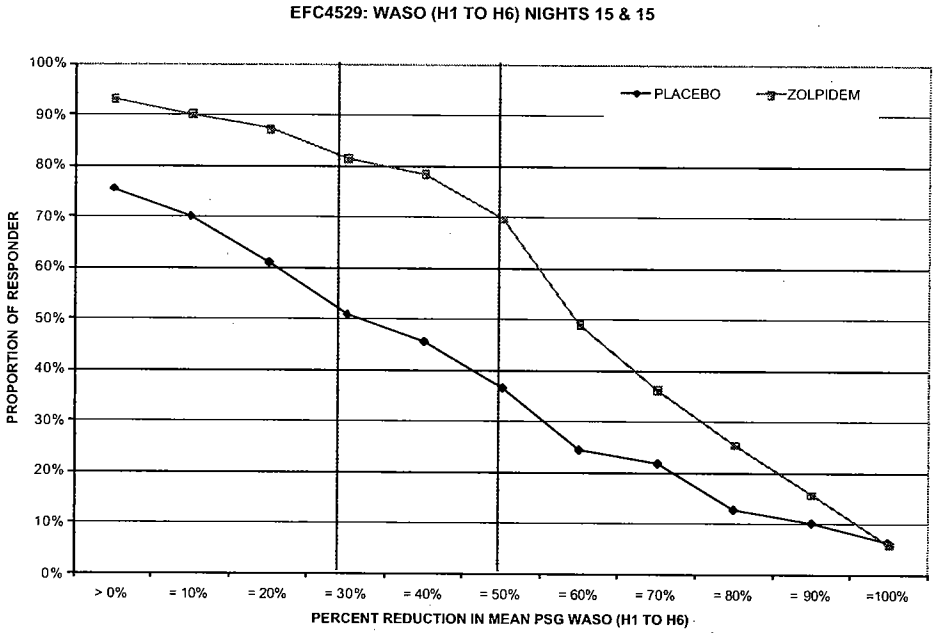


Figure 5: Response Profile at Nights 1 and 2 using PSG WASO during the first 8 hours after lights-out - ITT Population with NO MAJOR DEVIATIONS

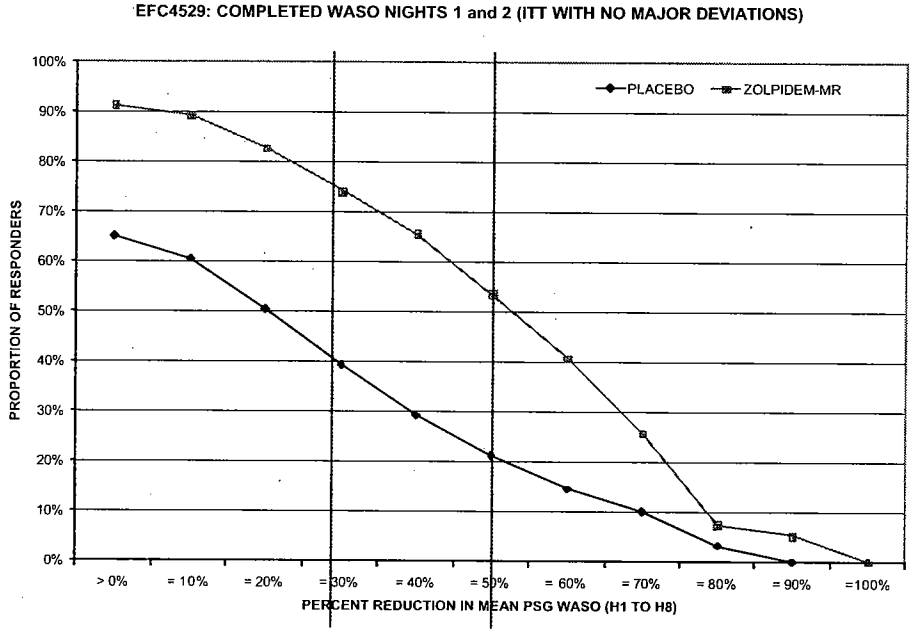


Figure 6: Response Profile at Nights 1 and 2 using PSG WASO during the first6 hours after lights-out - ITT Population with NO MAJOR DEVIATIONS

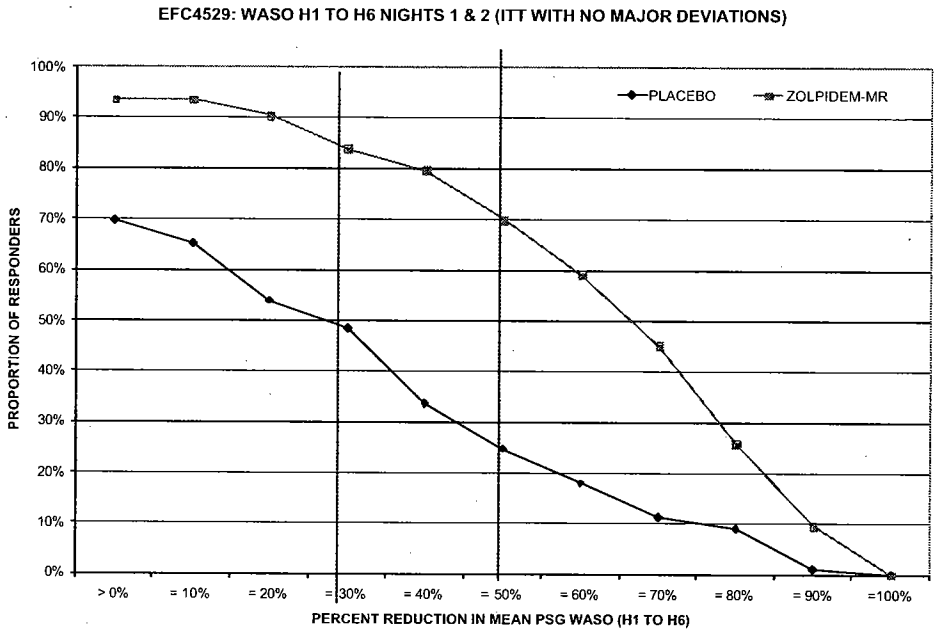


Figure 7: Response Profile at Nights 15 and 16 using PSG WASO during the first 8 hours after lights-out - ITT Population with NO MAJOR DEVIATIONS

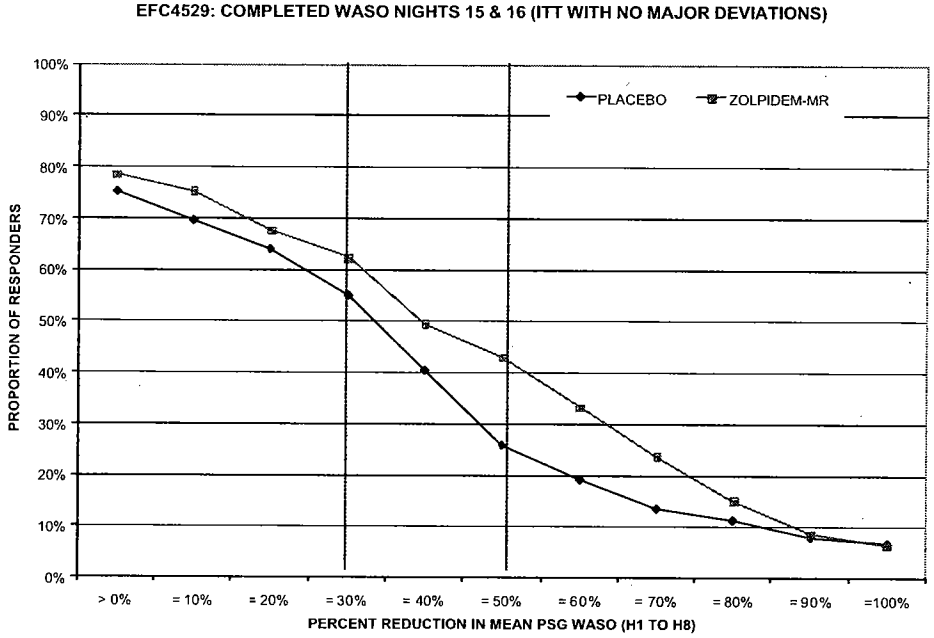
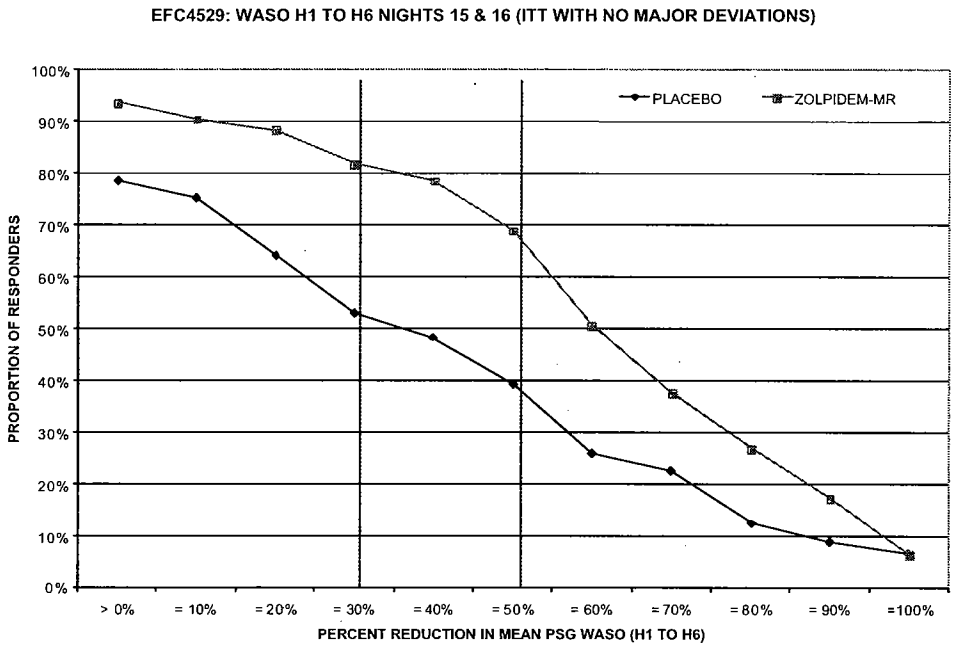


Figure 8: Response Profile at Nights 15 and 16 using PSG WASO during the first 6 hours after lights-out - ITT Population with NO MAJOR DEVIATIONS



EFC4530

Similar to EFC4529, Study EFC4530 was a randomized, double-blind, multi-center, placebo-controlled study to demonstrate the hypnotic efficacy of zolpidem-MR 6.25 mg by reducing the total time awake after sleep onset, as compared to placebo, in adult insomniac patients. The study lasted approximately 30 days for each patient, including a screening visit, a single-blind placebo run-in period, a three-week double-blind treatment period that includes two consecutive nights (N1 and N2) of PSG in a sleep laboratory, 12 nights of outpatient treatments, two consecutive nights (N15 and N16) of PSG in a sleep laboratory, five more nights of outpatient treatment, and lastly, a single-blind placebo run-out period.

A sample size of 100 patients per group was considered to be sufficient to detect a treatment difference (versus a placebo) in PSG WASO of 20 minutes (SD = 45 minutes) with a power at least 80%, a type-I error probability of 5% and a 2-sided comparison. This sample size of 100 patients per group takes into account a maximum of 4% possible missing data and 10% non-available data due to possible drop-outs (for the analysis on N15 and N16). The standard deviation (SD) was estimated based on a subgroup of patients included in a previous study (NDA-LSH17) with PSG WASO at least 40 minutes on the mean of the two baseline nights. A 20-minute difference between treatment groups for PSG WASO was considered to be clinically meaningful.

A total of 396 patients were screened in the study of whom 191 were not randomized. The main reason for screen failure was "inclusion or exclusion not respected" in 161 out of 191 patients

(84%). Of the 205 patients randomized to the study, 106 were randomized to the placebo group, and 99 were randomized to the zolpidem-MR 6.25 mg group (

Table 9). Patients were recruited from 40 centers (5 centers in Argentina, 7 in Canada, 4 in France, 6 in Germany, 2 in Mexico, and 16 centers in the United States).

Out of 205 patients, 7 patients (3%) withdrew from the study: 2/106 (2%) in the placebo group and 5/9 (5%) in the zolpidem-MR 6.25 mg group. The most frequent specified reason for premature withdrawal was investigator/subject's request [1 (1%) in the placebo and 3 (3%) in the zolpidem-MR 6.25 mg group]. Furthermore, 24 patients (15 in the placebo and 9 in the zolpidem-MR 6.25 mg group) were not included in the PP population.

Of the 205 patients who were randomized, all were exposed to the investigational product. However, for the PSG parameters, only 203 patients were analyzed in the ITT population because of missing central readings of PSG for one French center.

Table 9: Disposition of Patients

	Total	Active	Placebo
Screened	396		
Non-randomized Patients	191 (48.2%)		
Inclusion/exclusion criteria not respected	161 (84.3%)		
Adverse event	2 (1.0%)		
Withdrawal of consent	19 (9.9%)		
Lost to follow-up	1 (0.5%)		
Other	8 (4.2%)		
Randomized (Intent-to-Treat)	205	99	106
Completed	196	94	102
Discontinued	7 (3%)	5 (5%)	2 (2%)
Disease progression/lack of efficacy	1	1	0
Adverse event	1	1	0
Poor compliance to protocol	1	0	1
Investigator/subject's request	4	3	1
Subject's loss to follow-up	0	0	0
Other reason	0	0	0
Missing central readings of PSG	2	0	2
Per Protocol Population	181	90	91

The majority (57%) of the exposed population was female. The mean age (±SD) for the combined study groups was 70 ± 5 years, ranging from 64 to 87 years of age. The demographic characteristics (e.g. race, age, BMI) of patients who participated in this study were comparable between the treatment groups.

The mean duration of the current episode of insomnia was 163 ± 158 months in the placebo group, and 145 ± 146 months in the zolpidem-MR 6.25 mg group.

At baseline, patients had a mean WASO (1 to 6 hours) of 68:48 ± 33:36 min:sec, a mean WASO (1 to 8 hours) of 113:06 ± 44:00 min:sec, a mean total sleep time (TST) of 335:46 ± 50:41 min:sec, a mean latency to persistent sleep (LPS) of 36:16 ± 26:08 min:sec, and a mean number of nocturnal awakenings of 12 ± 4 for the combined study groups. Other baseline characteristics are summarized in Table 10.

Table 10: Summary of Patient's PSG Results and Sleep Morning Questionnaire at Screening - Exposed Population

		Placebo (N=106)	Zolpidem-MR 6.25 mg (N=99)	Total (N=205)
TST (min:sec)	n	104	99	203
	Median	341:15	347:00	343:00
	Mean (SD)	335:13 (51:54)	336:21 (49:38)	335:46 (50:41)
	Min - Max	122:00 - 432:15	171:45 - 436:15	122:00 - 436:15
WASO H1 to H6 (min:sec)	n	104	99	203
	Median	64:23	62:45	62:45
	Mean (SD)	70:15 (33:37)	67:16 (33:41)	68:48 (33:36)
	Min - Max	9:00 - 166:30	14:00 - 205:15	9:00 - 205:15
Total WASO (min:sec)	n	104	99	203
	Median	109:38	104:00	106:30
	Mean (SD)	113:22 (41:52)	112:48 (46:20)	113:06 (44:00)
	Min - Max	27:15 - 205:45	21:15 - 294:15	21:15 - 294:15
LPS (min:sec)	n	104	99	203
	Median	28:45	31:30	29:30
	Mean (SD)	35:43 (27:58)	36:52 (24:10)	36:16 (26:08)
	Min - Max	1:45 - 182:15	5:15 - 124:15	1:45 - 182:15
Number of awakenings	n	104	99	203
	Median	12	11	11
	Mean (SD)	12.1 (4.1)	10.8 (3.4)	11.5 (3.8)
	Min - Max	5 - 28	2 - 21	2 – 28

		Placebo (N=106)	Zolpidem-MR 6.25 mg (N=99)	Total (N=205)
Duration of sleep (min:sec)	n	105	99	204
	Median	320:00	330:00	322:30
	Mean (SD)	307:11 (87:03)	318:00 (86:01)	312:26 (86:31)
	Min - Max	5:00 - 480:00	90:00 - 600:00	5:00 - 600:00
Time spent awake after falling asleep (min:sec)	n	105	99	204
	Median	60:00	75:00	60:00
	Mean (SD)	83:06 (76:33)	82:07 (68:10)	82:38 (72:26)
	Min - Max	0:00 - 475:00	0:00 - 360:00	0:00 - 475:00
Sleep onset latency (min:sec)	n	105	99	204
	Median	45:00	45:00	45:00
	Mean (SD)	62:54 (59:49)	56:00 (45:58)	59:33 (53:32)
	Min - Max	5:00 - 345:00	5:00 - 260:00	5:00 - 345:00
Number of awakenings	n	105	99	204
	Median	4	3	3
	Mean (SD)	4.1 (2.9)	6.2 (18.3)	5.1 (12.9)
	Min - Max	0 - 20	0 - 154	0 - 154
Quality of sleep	n	106	99	205
	Median	3.0	3.0	3.0
	Mean (SD)	3.0 (0.7)	2.8 (0.6)	2.9 (0.7)
	Min - Max	2 - 4	1 - 4	1 - 4

Source: CRS-BDY-EFC4530-EN-E01 page 49/121

Table 11 summarizes the results from the primary efficacy analysis.. As stated in the applicant's analysis plan, analysis of covariance (ANCOVA) with baseline value as covariate is the analysis method for all PSG parameters in the primary and secondary outcomes. This decision was made before the blind was broken. On N1/N2, the mean total WASO during the first 6 hours decreased

(improved) from baseline (screening) by 6:59 and 32:41 min:sec in the placebo and zolpidem-MR 6.25 mg groups, respectively. The difference between treatment groups was statistically significant using ANCOVA analysis adjusting for baseline PSG WASO (p=<0.0001). Difference in treatment groups was also statistically significant (p<0.0001) on PSG WASO during the first 8 hours. On N15/N16, the mean total WASO decreased (improved) from baseline by 6:56 and 18:22 min:sec in the placebo and zolpidem-MR 6.25 mg groups, respectively. The difference between treatment groups was also statistically significant using ANCOVA analysis adjusting for baseline PSG WASO (p=0.0042). However, like Study EFC4529, treatment groups were comparable based on the mean change in PSG WASO during the first 8 hours.

Table 11: Results on the ANCOVA analysis for the PSG WASO data, Zolpidem-MR 12.5 mg versus Placebo - ITT Population

	N	Placebo	Active	Mean Diff	95% CI	p-value
WASO (Hours 1 to 6)						
Nights 1, 2	203	-6:59	-32:41	-25:42	(-32:19, -19:05)	<0.0001
Nights 15, 16	199	-6:56	-18:22	-11:27	(-19:14, -3:39)	0.0042
WASO (Hours 1 to 8)						
Nights 1, 2	203	-6:40	-33:23	-26:43		<0.0001
Nights 15, 16	199	-7:49	-15:00	-7:11		0.1485

Supportive efficacy analyses were conducted by the applicant (post-hoc) in order to better define the effects of the study treatment on WASO. This includes per-hour analyses of PSG WASO, as well as analyses on different parts of the nights divided into three parts (first 3 hours, middle 3 hours, and last 2 hours) using ANCOVA adjusting for baseline PSG WASO. The results are summarized in Table 12 and Table 13. The results provided showed apparent improvements in mean PSG WASO from baseline on Nights 1 and 2 across different hours/parts of the nights at least from Hour 2 up to Hour 6, and in mean PSG WASO from baseline on Nights 15 and 16 from Hour 2 up to Hour 4. Accounting for multiplicity, there still appeared to be statistical difference between the treatment groups on Nights 1 and 2 at Hours 2 to 6, and on Nights 15 and 16 at Hours 3 and 4 (Table 13).

Table 12: Results of the ANCOVA for the PSG WASO during Parts of the Night - ITT Population

	N	Placebo	Active	Mean Diff	95% CI	p-value
WASO H1 to H3						
Nights 1, 2	203	-1:43	-12:47	-11:04	(-14:20, -7:47)	<0.0001
Nights 15, 16	199	-1:40	-8:59	-7:20	(-11:04, -3:35)	0.0001
WASO H4 to H6						
Nights 1, 2	203	-5:09	-20:00	-14:51	(-20:25, -9:16)	<0.0001
Nights 15, 16	199	-5:02	-9.38	-4:36	(-11:32, 2:27)	0.2003
WASO H7 to H8						
Nights 1, 2	203	0:20	-0.46	-1:07	(-7:09, 4:54)	0.7227
Nights 15, 16	199	-1:00	3:32	4:32	(-1:12, 10:16)	0.1201

Table 13: Results of the ANCOVA of the comparison of the PSG WASO per hour data, Zolpidem-MR 12.5mg versus Placebo - ITT Population

Table (11.1.1.2.2) 1 - Results of the ANCOVA for the PSG WASO per hour (min:sec), zolpidem-MR 6.25 mg versus placebo - ITT population

Parameter	Time	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1	Nights 1, 2	203	0:03	-0:37	-0:39	[-1:32 ; 0:13]	(1,200)	0.1434
	Nights 15, 16	199	0:21	-0:13	-0:34	[-1:29 ; 0:20]	(1,196)	0.2148
WASO H2	Nights 1, 2	203	-1:07	-5:30	-4:24	[-5:57 ;-2:50]	(1,200)	<.0001 *
	Nights 15, 16	199	-1:23	-4:01	-2:38	[-4:34 ;-0:42]	(1,196)	0.0080 *
WASO H3	Nights 1, 2	203	-0:35	-6:45	-6:09	[-8:14 ;-4:05]	(1,200)	<.0001 *
	Nights 15, 16	199	-0:38	-4:46	-4:09	[-6:13 ;-2:04]	(1,196)	0.0001 *
WASO H4	Nights 1, 2	203	-2:05	-7:47	-5:42	[-8:06 ;-3:18]	(1,200)	<.0001 *
	Nights 15, 16	199	-2:31	-6:48	-4:17	[-6:45 ;-1:50]	(1,196)	0.0007 *
WASO H5	Nights 1, 2	203	-2:03	-7:08	-5:05	[-7:38 ;-2:32]	(1,200)	0.0001 *
	Nights 15, 16	199	-1:58	-2:00	-0:02	[-3:25 ; 3:20]	(1,196)	0.9815
WASO H6	Nights 1, 2	203	-0:51	-5:16	-4:25	[-7:37 ;-1:13]	(1,200)	0.0070 *
	Nights 15, 16	199	-0:16	-1:08	-0:52	[-4:40 ; 2:56]	(1,196)	0.6547
WASO H7	Nights 1, 2	203	0:12	-0:22	-0:34	[-4:25 ; 3:17]	(1,199)	0.7730
	Nights 15, 16	199	-0:37	0:28	1:05	[-2:26 ; 4:36]	(1,196)	0.5428
WASO H8	Nights 1, 2	203	-0:00	-0:18	-0:17	[-4:02 ; 3:27]	(1,200)	0.8782
	Nights 15, 16	199	-0:32	3:14	3:46	[-0:24 ; 7:56]	(1,196)	0.0758

«ref=PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/t11l1psg.sas OUT= OUTPUT/t11l1psg_4.ged (25NOV2003 - 13:29)

*: p<0.05

The results for the secondary outcomes are presented in Table 14 in the order of priority. On N1/N2, the adjusted mean SE, and the adjusted mean LPS improved from baseline in both treatment groups, favoring the zolpidem-MR 6.25 mg group (i.e. mean difference in SE = 0.073, mean difference in LPS = 10:15). Meanwhile, the mean quality of sleep on Days 1 and 2 improved favoring the zolpidem-MR 6.25 mg treated group with mean difference = 0.35.

On N15/N16, the adjusted mean SE, and the adjusted mean LPS also improved from baseline in both treatment groups, favoring the zolpidem-MR 6.25 mg group (i.e. mean difference in SE = 0.023, mean difference in LPS = 5:49). Although there was some improvement from baseline in the mean quality of sleep in both zolpidem-MR 6.25 mg group and placebo group, these improvements were comparable in both treatment groups (mean difference = 0.01).

Table 14: Results of the ANCOVA of the comparison of the Secondary Outcome Variables, Zolpidem-MR 12.5mg versus Placebo - ITT Population

	N	Placebo	Active	Mean Diff	95% CI	p-value
PSG Sleep Efficiency (SE)						
Nights 1, 2	203	0.030	0.102	0.073	(0.052, 0.093)	<0.0001
Nights 15, 16	199	0.035	0.059	0.023	(-0.00, 0.046)	0.0509
PSG Latency to Persistent Sleep (LPS)						
Nights 1, 2	203	-6:55	-17:10	-10:15	(-15:25, -5:04)	0.0001
Nights 15, 16	199	-8:30	-14:18	-5:49	(-10:54, -0:43)	0.0255
Quality of Sleep						
Days 1, 2	205	-0.25	-0.60	-0.35	(-0.52, -0.18)	0.0001
Days 15, 16	201	-0.30	-0.29	-0.01	(-0.18, 0.19)	0.9319

The results from the analysis of other secondary outcomes suggest that on Days 1 and 2, the refreshing quality of sleep, subjective WASO, subjective TST, and subjective SOL improved in the zolpidem-MR 6.25 mg group compared to the placebo. On Days 15 and 16, it appeared that both treatment groups were comparable in terms of the refreshing quality of sleep, subjective WASO, subjective TST, subjective SOL, subjective and objective number of awakenings, and disturbances in daily activities (Table 15).

The percentage of patients who considered that the study medication helped them to sleep was also greater in the zolpidem-MR 6.25 mg group than in the placebo at Days 2 and 15.

Table 15: Results of the ANOVA of the comparison of Other Secondary Outcome Variables, Zolpidem-MR 12.5mg versus Placebo - ITT Population

	N	Placebo	Active	Mean Diff	95% CI	p-value
Patient Global Impression (%) using Chi-Square						
Day 2	200	54.8	70.8			0.0193
Day 15	201	48.6	65.6			0.0148
Refreshing Quality of Sleep						
Days 1, 2	205	-0.2	-0.5	0.32	(0.13, 0.52)	0.0014
Days 15, 16	201	-0.1	-0.3	0.16	(-0.04, 0.35)	0.1081
Subjective Wake time after sleep (WASO)						
Days 1, 2	203	-3:22	-26:51	23:29	(5:39, 41:19)	0.0101
Days 15, 16	199	-0:25	-14:29	14:04	(-5:42, 33:50)	0.1620
Subjective Total Sleep Time						
Days 1, 2	204	22:19	55:08	-32:50	(-51:27, -14:12)	0.0006
Days 15, 16	200	28:31	43:39	-15:08	(-39:05, 8:49)	0.2143
Subjective Sleep Onset Latency (SOL)						
Days 1, 2	204	-9:10	-24:09	14:59	(0:32, 29:26)	0.0421
Days 15, 16	200	-24:45	-23:30	-1:15	(-15:35, 13:05)	0.8636
PSG Number of Awakenings (ANCOVA)						
Nights 1, 2	203	-0.5	-1.6	-1.1	(-1.9, -0.4)	0.0046
Nights 15, 16	199	-0.8	-0.3	0.6	(-0.3, 1.5)	0.2513
Subjective Number of Awakenings						
Days 1, 2	204	-0.3	-3.5	3.27	(-0.28, 6.38)	0.0710
Days 15, 16	200	-1.1	-3.4	2.23	(-1.00, 5.46)	0.1746
Disturbances in daily activities						
Nights 1, 2	205	-0.2	-0.1	-0.09	(-0.29, 0.11)	0.3866
Nights 15, 16	201	-0.2	-0.1	-0.07	(-0.34, 0.20)	0.5964

I also carried out responder analysis to assess the sensitivity of the Observed Cases analysis performed by the sponsor in handling missing data. The responder analysis is based on percent decrease in mean pain score from baseline. The percent decrease was classified in 10-percent increments (e.g. =10%, =20%,..., =100% pain reduction) giving cumulative distribution functions of pain reduction by treatment groups. In this analysis, patients who withdrew from the study before Night 15 regardless of the reason for withdrawal were classified as non-responders at N15/N16.

The proportions of responders based on PSG WASO recording during the first 8 hours and during the first 6 hours at Nights 1 and 2, and Nights 15 and 16, for all the various definitions of responder considered are presented (Figures 9 – 12). Inspection of these graphs suggests that there are apparent differences in the proportion of responders between the two treatment groups during the first
8 hours and during the first 6 hours at Nights 1 and 2, favoring zolpidem-MR 6.25 mg group. Although there are differences in the proportion of responders between the treatment groups during the first 8 hours at Nights 15 and 16, these differences became more pronounced when PSG WASO during the first 6 hours was plotted. Overall, higher proportions of subjects in the zolpidem-MR 6.25 mg group were treatment responders compared to the placebo-treated group when different definitions of responder (based on different percent pain reduction) were used. These results were consistent with the Observed Cases Analyses.

Figure 9: Response Profile at Nights 1 and 2 using PSG WASO during the first 8 hours after lights-out - ITT Population

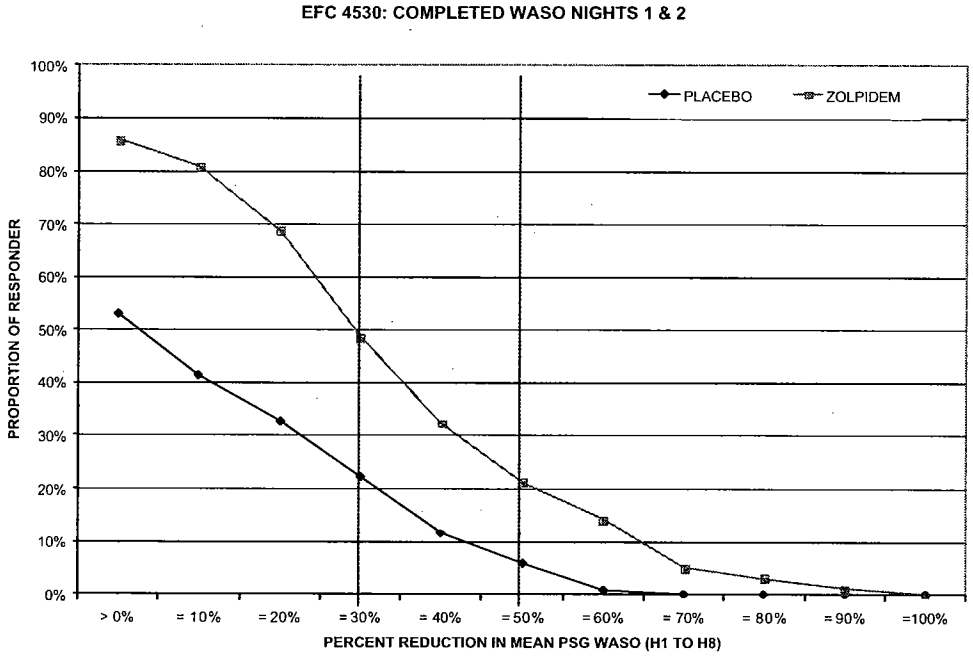


Figure 10: Response Profile at Nights 1 and 2 using PSG WASO during the first6 hours after lights-out - ITT Population

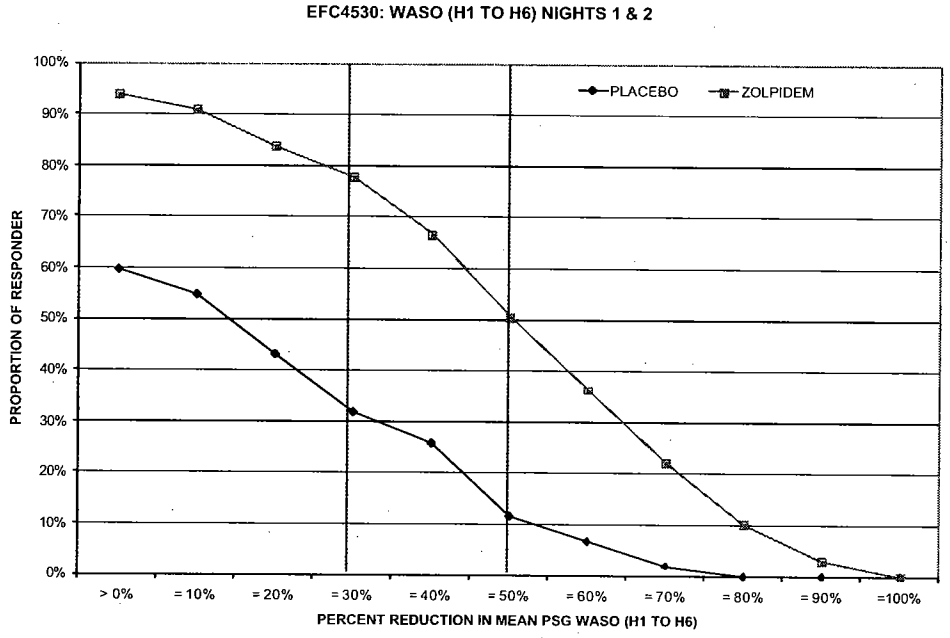


Figure 11: Response Profile at Nights 15 and 16 using PSG WASO during the first 8 hours after lights-out - ITT Population

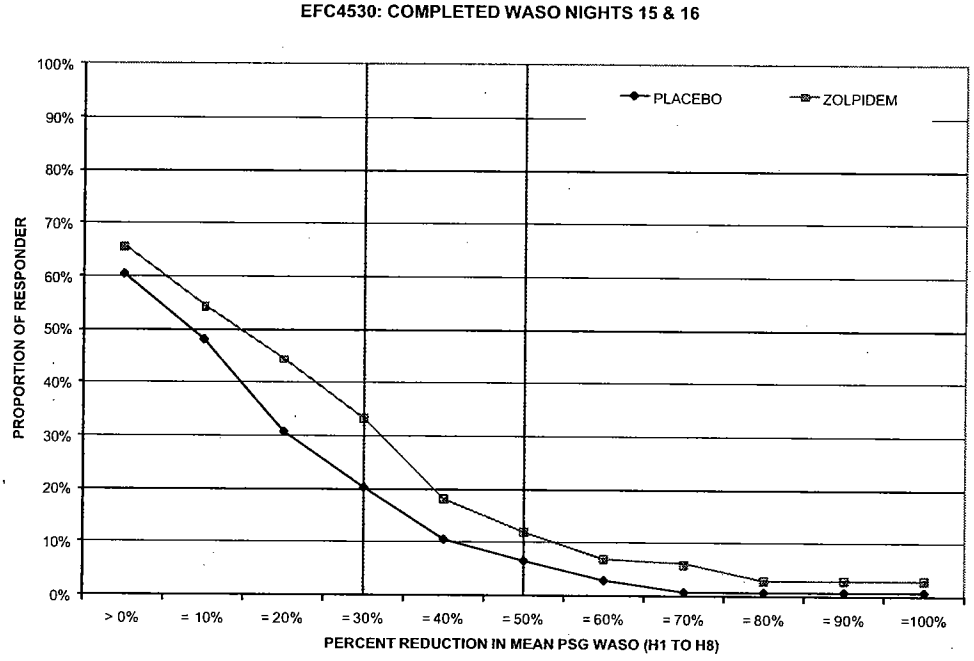
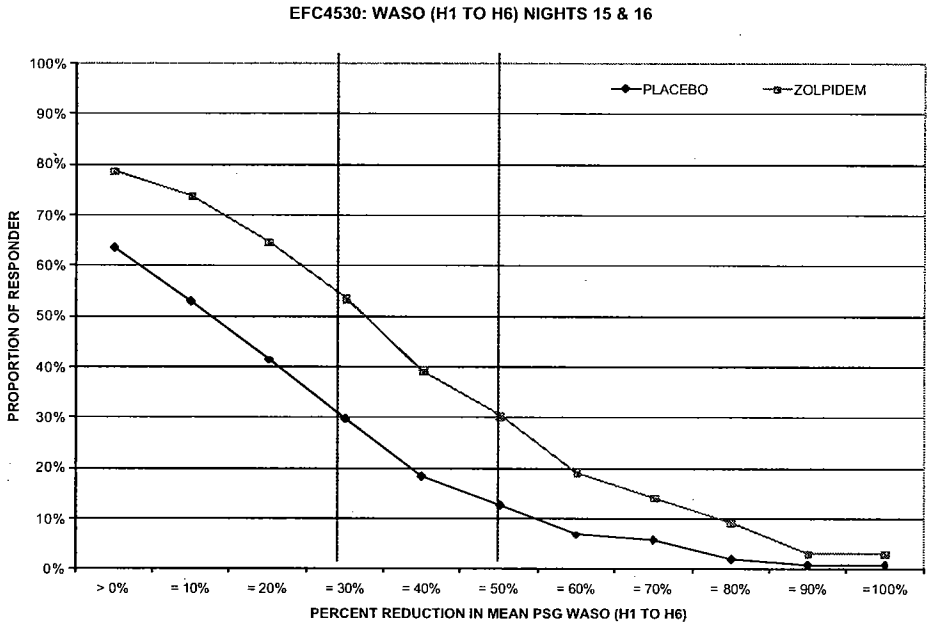


Figure 12: Response Profile at Nights 15 and 16 using PSG WASO during the first 6 hours after lights-out - ITT Population



3.2 EVALUATION OF SAFETY

Safety was assessed by the applicant in both studies using a clinical evaluation, vital signs, and a review of adverse events (AEs). An assessment of residual effects [as assessed by digit symbol substitution test (DSS), the Rey auditory verbal learning test (RAVLT), and two questions on the morning questionnaire], and the rebound effect (assessed by analyzing WASO, SE and LPS results after abrupt discontinuation of study treatment on Nights 22 and 23) were also conducted by the applicant as part of safety evaluation. A detailed review of the safety profile of zolpidem-MR 12.5 mg and 6.25 mg doses can be found in Dr. Elizabeth McNeil's review.

A summary of the residual and rebound effects on Studies EFC4529 and EFC4530 is presented below. In Study EFC4529, the objective assessment of next day residual measured by psychometric tests (DSST and RAVLT) showed no noticeable decrease in performance in zolpidem-MR 12.5 mg. A practice effect was observed in both treatment groups and this effect was smaller in the zolpidem-MR 12.5 mg group compared with the placebo group on Days 1 and 2. In Study EFC4530, the objective assessment of next day residual measured by psychometric tests (DSST and RAVLT) showed no marked decrease in performance in zolpidem-MR 6.25 mg. A practice effect was observed in both treatment groups for the DSST and this effect was smaller in the zolpidem-MR 6.25 mg group compared to the placebo group on Days 1 and 2. No residual effect between treatment groups was observed on Days 15 and 16 in both studies based on objective assessments.

In terms of subjective assessments on patient questionnaires (i.e. ability to concentrate in the morning or sleepiness in the morning), there was no evidence of next day residual either on Days 1 and 2, or Days 15 and 16 in both studies (EFC4529 and EFC4530).

Both studies observed rebound effects after the first night of abrupt discontinuation of zolpidem-MR 12.5 mg for WASO, SE, and LPS and of zolpidem-MR 6.25 mg for WASO and SE. There was also worsening on LPS in subjects taking zolpidem-MR 6.25 mg after the first night of abrupt discontinuation. On the second night (N23), there appears to be no worsening on WASO, SE, and LPS compared with the results at baseline in the placebo, zolpidem-MR 12.5 and in the zolpidem-MR 6.25 group. However, the improvement on WASO and SE (as well as slight improvement in LPS) favored the placebo group in Study 4529, and in Study 4530, the improvement on LPS (and slight improvement on WASO and SE) favored the placebo group, as well.

Table 16: Summary of one-way ANOVA analyses of Rebound Effects and Residual Effects - Zolpidem-MR 12.5 mg versus Placebo - Exposed Population (EFC 4529)

	N	Placebo	Active	Mean Diff	95% CI	p-value
RESIDUAL EFFECTS						
DSST						
Days 1, 2	211	2.3 (6.3)	0.4 (5.9)	1.88	(0.23, 3.54)	0.0262
Days 15, 16	198	3.2 (7.1)	3.0 (6.7)	0.27	(-1.67, 2.21)	0.7838
RAVLT (I to V)						
Days 1, 2	211	0.6 (1.1)	0.2 (1.2)	0.35	(0.03, 0.67)	0.0335
Days 15, 16	198	0.4 (1.3)	0.4 (1.2)	-0.01	(-0.36, 0.34)	0.9614
RAVLT (VI)						
Days 1, 2	211	0.4 (2.0)	-0.4 (2.0)	0.79	(0.25, 1.33)	0.0044
Days 15, 16	198	0.15 (2.1)	0.03 (2.0)	0.12	(-0.45, 0.69)	0.6819
Sleepiness in the Morning						
Days 1, 2	212	49.5 (24.0)	50.3 (23.2)	-3.4	(-9.42, 2.63)	0.2673
Days 15, 16	199	49.4 (26.2)	52.9 (23.8)	-4.08	(-11.21, 3.05)	0.2601
Ability to Concentrate in the AM						
Days 1, 2	211	2.6 (0.7)	2.4 (0.6)	0.23	(0.08, 0.38)	0.0030
Days 15, 16	198	2.6 (0.7)	2.5 (0.6)	0.12	(-0.07, 0.31)	0.2132
REBOUND EFFECT						
PSG WASO						
Night 22	190	-13:27 (46:42)	26:25 (70:44)	39:52	(22:49, 56:55)	<0.0001
Night 23	186	-28:39 (41:06)	-10:33 (56:33)	18:06	(3:52, 32:21)	0.0130
SLEEP EFFICIENCY (SE)						
Night 22	191	0.051 (0.14)	-0.086 (0.19)	-0.137	(-0.185, -0.089)	<0.0001
Night 23	186	0.085 (0.11)	0.033 (0.15)	-0.052	(-0.090, -0.015)	0.0068
Latency to Persistent Sleep (LPS)						
Night 22	190	-12:03 (45:15)	10:40 (48:23)	22:43	(9:19, 36:07)	0.0010
Night 23	186	-13:42 (33:51)	-7:40 (39:40)	6:02	(-4:37, 16:41)	0.2652

Table 17: Summary of one-way ANOVA analyses of Rebound Effects and Residual Effects - Zolpidem-MR 6.25 mg versus Placebo - Exposed Population (EFC 4530)

	N	Placebo	Active	Mean Diff	95% CI	p-value
RESIDUAL EFFECT						
DSST						
Days 1, 2	204	2.1 (3.7)	0.66 (4.1)	1.42	(0.33, 2.5)	0.0106
Days 15, 16	200	4.2 (4.6)	2.9 (4.6)	1.24	(-0.04, 2.53)	0.0584
RAVLT (I to V)						
Days 1, 2	202	0.29 (1.3)	0.21 (1.2)	0.08	(-0.26, 0.42)	0.6561
Days 15, 16	198	0.32 (1.2)	0.27 (1.2)	0.05	(-0.28, 0.39)	0.7494
RAVLT (VI)						
Days 1, 2	202	-0.36 (1.9)	-0.39 (2.2)	0.02	(-0.54, 0.59)	0.9313
Days 15, 16	198	-0.20 (1.87)	-0.3 (2.1)	0.10	(-0.44, 0.65)	0.7148
Sleepiness in the Morning						
Days 1, 2	205	2.1 (20.9)	4.2 (24.4)	-2.13	(-8.37, 4.12)	0.5027
Days 15, 16	201	-1.3 (23.2)	2.1 (27.4)	-3.37	(-10.41, 3.67)	0.3467
Ability to Concentrate in the Morning						
Days 1, 2	204	0.11 (0.6)	-0.01 (0.6)	0.11	(-0.05, 0.27)	0.1594
Days 15, 16	200	0.14 (0.6)	0.12 (0.6)	0.02	(-0.15, 0.20)	0.8008
REBOUND EFFECT						
PSG WASO						
Night 22	193	-8:23 (46:13)	29:26 (61:29)	37:50	(22:29, 53:10)	<0.0001
Night 23	194	-12:23 (49:42)	-8:55 (57:10)	3:28	(-11:41, 18:36)	0.6522
SLEEP EFFICIENCY (SE)						
Night 22	193	0.02 (0.11)	-0.08 (0.15)	-0.102	(-0.14, -0.065)	<0.0001
Night 23	194	0.06 (0.12)	0.03 (0.14)	-0.030	(-0.066, 0.006)	0.1031
LATENCY TO PERSISTENT SLEEP (LPS)						
Night 22	193	0:24 (39:25)	10:45 (53:31)	10:21	(-2:54, 23:36)	0.1251
Night 23	194	-15:33 (27:01)	-5:04 (38:06)	10:30	(1:12, 19:47)	0.0271

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

4.1 SEX, RACE, AND AGE

Separate analyses by age, race, and sex were carried out in both studies using Observed Cases analyses. The results based on the subgroup population across different studies are so variable that interactions are difficult to interpret.

In Study EFC4529, no sex, race, or age effects were observed after conducting subgroup analyses.

Table 18: Descriptive Statistics on the Mean Change in PSG WASO (Hours 1 to 8) by Sex and Race - Zolpidem-MR 6.25 mg versus Placebo – ITT Population with NO Major Deviations (EFC 4529)

		Placebo			Zolpidem-MR 12.5 mg	
	N	Mean (SE)	Median	n	Mean (SE)	Median
N1/N2	89	-19:16 (43:15)	-19:45	93	-40:54 (31:51)	-38:00
Sex						
Male	45	-20:23 (40:15)	-19:45	36	-40:05 (32:04)	-38:08
Female	44	-18:08 (46:34)	-19:23	57	-41:25 (31:59)	-38:00
Race						
Caucasian	83	-18:00 (42:17)	-19:45	83	-40:13 (30:21)	-37:45
Other	6	-36:55 (56:40)	-32:15	10	-46:32 (44:00)	-54:38
N15/N16	83	-22:51 (43:47)	-26:45	87	-25:17 (40:16)	-29:15
Sex						
Male	42	-17:15 (41:17)	-22:45	34	-18:15 (51:02)	-20:45
Female	41	-28:38 (45:59)	-27:15	53	-29:47 (31:15)	-31:00
Race						
Caucasian	79	-21:42 (43:52)	-26:45	78	-26:49 (39:19)	-30:45
Other	4	-45:34 (40:27)	-28:00	9	-12:02 (48:21)	-12:00

In Study EFC4530, no sex, race, or age effects were observed after conducting subgroup analyses on nights 1 and 2, or on nights 15 and 16. Although the interaction between treatment group and age group was non-significant on N15/N16 with or without adjusting for baseline PSG WASO (hours 1 to 6), the subgroup containing subjects who were aged 70 to 74 did not appear to have a treatment difference while the total population was shown to have a treatment difference. However, because there are substantial statistical uncertainties due to lack of power and small sample size in each subgroup, it is difficult to be confident whether there is real age variation in the effect or there is not.

Table 19: Descriptive Statistics on the Mean Change in PSG WASO (Hours 1 to 6) by Country and Sex - Zolpidem-MR 6.25 mg versus Placebo – ITT Population (EFC 4530)

		Placebo			Zolpidem-MR 12.5 mg	
	N	Mean (SE)	Median	n	Mean (SE)	Median
N1/N2	104	-7:44 (32:25)	-6:45	99	-31:53 (26:07)	-28:00
Sex						
Male	47	-11:18 (32:06)	-13:15	39	-34:52 (22:04)	-34:15
Female	57	-4:47 (32:41)	-5:30	60	-29:57 (28:27)	-23:08
Age Group						
< 70	53	-0:40 (32:22)	-3:45	50	-28:46 (24:23)	-24:38
70 – 74	35	-17:47 (29:02)	-16:15	33	-32:25 (29:13)	-28:00
= 75	16	-9:09 (43:30)	-14:53	16	-40:31 (24:04)	-36:38
Race Group						
Caucasian	99	-8:09 (32:51)	-8:15	94	-32:40 (26:29)	-29:45
Others	5	0:36 (23:01)	-0:45	5	-17:21 (11:14)	-22:45
N15/N16	103	-7:29 (31:04)	-7:30	96	-17:46 (31:17)	-18:30
Sex						
Male	47	-9:08 (32:04)	-8:45	39	-13:48 (28:07)	-16:30
Female	56	-6:06 (30:26)	-7:08	57	-20:30 (33:15)	-19:00
Age Group						
< 70	53	-3:31 (28:33)	-4:00	50	-16:03 (27:09)	-17:15
70 – 74	34	-13:48 (32:53)	-15:53	31	-15:27 (35:27)	-15:30
= 75	16	-7:15 (34:53)	-8:30	15	-28:20 (35:02)	-29:15
Race Group						
Caucasian	98	-8:25 (30:58)	-8:30	91	-18:19 (31:58)	-19:00
Others	5	10:39 (30:40)	13:00	5	-8:00 (11:15)	-8:30

4.2 OTHER SUBGROUPS AND SPECIAL POPULATIONS

Separate analyses by country were also carried out in both studies using Observed Cases analyses. Similarly, the results based on the subgroup population across different studies are so variable that interactions are difficult to interpret.

In Study EFC4529, no country effects were observed after conducting subgroup analyses at Nights 1 and 2, and at Nights 15 and 16. However, although the interaction between treatment group and country was non-significant on N15/N16 with or without adjusting for baseline PSG WASO, the direction of the treatment difference in Australia and in Canada is reversed from the result obtained for the total population. Because there are substantial statistical uncertainties due to lack of power and small sample size in each subgroup, it is difficult to be confident whether there is real geographical variation in the effect or there is not.

Table 20: Descriptive Statistics on the Mean Change in PSG WASO (Hours 1 to 8) by Country - Zolpidem-MR 6.25 mg versus Placebo – ITT Population with NO Major Deviations (EFC 4529)

	Placebo			Zolpidem-MR 12.5 mg		
	N	Mean (SE)	Median	n	Mean (SE)	Median
N1/N2	89	-19:16 (43:15)	-19:45	93	-40:54 (31:51)	-38:00
Country						
Australia	9	-29:57 (50:01)	-39:45	11	-45:04 (31:08)	-38:30
Canada	13	0:42 (35:57)	6:00	13	-29:20 (25:01)	-30:30
United States	67	-21:43 (43:05)	-21:00	69	-42:25 (33:00)	-42:45
N15/N16	83	-22:51 (43:47)	-26:45	87	-25:17 (40:16)	-29:15
Country						
Australia	8	-40:54 (42:02)	-44:00	11	-27:25 (41:14)	-21:15
Canada	12	-18:58 (50:12)	-25:08	13	-9:32 (32:53)	-18:15
United States	63	-21:18 (42:54)	-24:30	63	-28:10 (41:17)	-33:00

In Study EFC4530, no country effect was observed after conducting subgroup analyses on nights 1 and 2. In contrast, on nights 15 and 16, there appears to be a significant interaction between treatment group and the country effect as evidence by the descriptive statistics within each subgroup and by the test of interaction. From Table 21, the directions of the treatment difference in some of the country subgroups (e.g. France/Germany and Canada) are reversed from the result obtained for the total population. Again, because there are substantial statistical uncertainties due to lack of power and small sample size in each subgroup, these make the interaction difficult to interpret. Therefore it is difficult to be confident whether there is real demographic variation in the effect or there is not.

Table 21: Descriptive Statistics on the Mean Change in PSG WASO (Hours 1 to 6) by Country - Zolpidem-MR 6.25 mg versus Placebo – ITT Population (EFC 4530)

	Placebo			Zolpidem-MR 12.5 mg		
	N	Mean (SE)	Median	n	Mean (SE)	Median
N1/N2	104	-7:44 (32:25)	-6:45	99	-31:53 (26:07)	-28:00
Country						
Argentina/Mexico	11	0:40 (32:47)	9:45	7	-15:04 (23:24)	-16:30
France/Germany	18	-9:13 (29:50)	-3:30	15	-27:28 (33:15)	-25:45
Canada	24	-11:23 (32:47)	-14:00	25	-33:15 (24:59)	-33:45
United States	51	-7:18 (33:37)	-6:00	52	-34:46 (24:23)	-28:00
N15/N16	103	-7:29 (31:04)	-7:30	96	-17:46 (31:17)	-18:30
Country						
Argentina/Mexico	11	5:49 (41:04)	4:00	6	-31:43 (29:41)	-31:38
France/Germany	17	-20:56 (31:59)	-13:15	15	-20:44 (35:10)	-21:15
Canada	24	-11:08 (27:43)	-8:15	24	-5:24 (36:35)	-14:53
United States	51	-4:09 (28:52)	-7:00	51	-21:05 (26:26)	-19:00

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Three statistical issues appeared to be of concern in these two studies.

The first issue is on the interpretation of efficacy results in Study EFC4529. The applicant made it clear in the expanded statistical analysis plan (Appendix 16.1.9.1) and the report (CSR_BDF-EFC4529-EN-E01, pages 35-37) that one-way analysis of variance (ANOVA) is the method of analysis for the primary and secondary outcomes. Although the applicant did request to change the ANOVA method to analysis of covariance (ANCOVA) because of slope heterogeneity at baseline for the PSG parameters, this change was made after the blind was broken. In contrast, the applicant's analysis plan was clear in Study EFC4530. In this study, the applicant made an amendment to the protocol requesting modification of the primary endpoint analysis before the blind was broken, and this was accepted by the Agency. The changes were replacement of total WASO by WASO during the first 6 hours of the night, and replacement of the ANOVA by an ANCOVA for all the PSG parameters. All the other secondary parameters except the Patient's Global impression scales were analyzed using a one-way ANOVA.

In light of this issue, both studies showed the immediate hypnotic effect of zolpidem-MR 12.5 mg and zolpidem-MR 6.25 compared to placebo. The primary measure of efficacy was the mean change of Polysomnography - Wake after Sleep Onset (PSG WASO) recordings on Nights 1 and 2 during the first 8 hours after lights-out in Study EFC 4529 and during the first 6 hours after lights-out in Study EFC 4530. However, Study EFC4529 failed to demonstrate persistence of hypnotic effect in zolpidem-MR 12.5 mg. The primary measure of efficacy in this study was the mean change of Polysomnography - Wake after Sleep Onset (PSG WASO) recordings on Nights 1 and 2 during the first 8 hours after lights-out. Although the direction (i.e. zolpidem-MR 12.5 mg is superior to placebo) in N15/N16 was consistent with N1/N2, the difference between the treatment groups was not statistically significant. After conducting exploratory analyses in Study EFC4529, the applicant concluded that "Based on the information EFC4529, the analysis of WASO per hour showed an increased variability during the last part of the night (hours 7 and 8) in comparison to the first 6 hours of the night", thereby prompting the applicant to modify the primary efficacy measure in Study EFC4530. As expected, using PSG WASO during the first 6 hours, the applicant was able to demonstrate the persistence of hypnotic effect in zolpidem-MR 6.25 mg in Study EFC4530.

The second issue is on the stepdown procedure following a non-statistically significant result at Nights 15 and 16 in Study EFC4529. The applicant did not state any stopping procedure if the results from Nights 15 and 16 were not significant in the expanded statistical analysis plan (Appendix 16.1.9.1). As a result, the outcome from the secondary efficacy analyses in Study EFC4529 may not be correct even if it appears that there were improvements on other subjective and objective measurements such as sleep efficiency, latency to persistent sleep, quality of sleep, and number of awakenings, and also on patient's global impression score during the first two days (D1/D2) or two nights (N1/N2) of the double-blind phase in both studies, favoring zolpidem-MR. In contrast, both studies showed clear evidence that zolpidem-MR and placebo are not different in terms of other subjective and objective sleep measures during Nights 15 and 16 except for PSG latency to persistency sleep in Study EFC4530 and patient global impression in both studies.

The third issue is on the case of missing measurements on Nights 15 and 16 in which the applicant used the Observed Cases procedure. Although the applicant adhered to the Agency's suggestions about this problem, I performed additional sensitivity analysis that takes into account missing data on Nights 15 and 16 by conducting responder analysis. This method assumes that subjects who dropped out or had missing data were regarded as non-responders or failures. Note that there were no missing data on Nights 1 and 2. Applying responder analysis in these two studies generated consistent results with the one-way ANOVA in Study EFC4529 and ANCOVA analyses in Study EFC4530. Therefore, those who dropped out or had missing measurements did not affect the outcome of the two studies.

There is one non-statistical issue that was also addressed in the review. This is relevant to the study population in Study EFC4529 is the inclusion of subjects who had Mean PSG WASO on SN1 and SN2 > 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours, as well as those subjects whose study sites were not in compliance with GCP. There were 30 subjects who had these problems included in the analysis. Re-analysis of the primary efficacy outcome and the secondary outcomes using the reduced data showed no difference in the results when these 30 subjects were included in the analyses.

Other statistical findings include Next-Day Residual Effects and Rebound Effects. In terms of Next-Day Residual Effects, the objective assessment of next day residual measured by psychometric tests (DSST and RAVLT) showed no marked decrease in performance in zolpidem-MR 12.5 mg and zolpidem-MR 6.25 mg. Although residual effect was observed in both treatment groups from both Studies, this effect was smaller in the zolpidem-MR 12.5 mg group compared with the placebo group on Days 1 and 2. On the contrary, no residual effect was observed on Days 15 and 16 between treatment groups in both studies based on objective assessments. As part of the Applicant's labeling claim, next-day residual effects were also evaluated in three Pharmacodynamic studies (one in elderly adults and two in young adults). In these three studies, exploratory analyses of the psychomotor and cognitive test results demonstrated that zolpidem-MR 6.25 mg and zolpidem-MR 12.5 mg dose have no residual effects 8 hours post-dosing (see Appendix 6.2).

In terms of subjective assessments on patient questionnaires (i.e. ability to concentrate in the morning or sleepiness in the morning), there was no evidence of next day residual either on Days 1 and 2, or Days 15 and 16 in both studies (EFC4529 and EFC4530).

Both studies showed rebound effects after the first night of abrupt discontinuation of zolpidem-MR 12.5 mg for WASO, SE, and LPS and of zolpidem-MR 6.25 mg for WASO and SE. There was also worsening on LPS in subjects taking zolpidem-MR 6.25 mg after the first night of abrupt discontinuation. On the second night (N23), there appears to be no worsening on WASO, SE, and LPS compared with the results at baseline in the placebo, zolpidem-MR 12.5 mg and in the zolpidem-MR 6.25 mg group. However, the improvement on WASO and SE (as well as slight improvement in LPS) favored the placebo group in Study 4529, and in Study 4530, the improvement on LPS (and slight improvement on WASO and SE) favored the placebo group as well.

5.2 CONCLUSIONS AND RECOMMENDATIONS

I conclude that zolpidem-MR 12.5 mg and zolpidem-MR 6.25 mg are effective in providing *immediate* hypnotic effect during the first 6 to 8 hours after lights-out, by reducing the total wake time after sleep onset as measured by digital polysomnography (PSG). There is also strong evidence that zolpidem-MR improved sleep induction, (measured by latency to persistent sleep), sleep duration (measured by sleep efficiency), and quality of sleep during Nights 1 and 2.

There is evidence that both zolpidem-MR 12.5 mg and zolpidem-MR 6.25 are effective in providing *persistence* in hypnotic effect, by reducing WASO during the first 6 hours after lights-out to patients with primary insomnia. However, among the main secondary variables analyzed, only sleep induction (measured by latency to persistent sleep) in Study EFC4530 appeared to be different, favoring zolpidem-MR group.

Analyses on next-day residual effects and rebound effects were conducted in Study EFC4529 and Study EFC4530. The result showed no evidence of next-day residual effects (measured either objectively or subjectively). In terms of rebound effects, both studies observed rebound effects after the first night of abrupt discontinuation of zolpidem-MR 12.5 mg and of zolpidem-MR 6.25 mg. On the second night (N23), there appears to be no worsening on WASO, SE, and LPS compared with the results at baseline in the placebo, zolpidem-MR 12.5 and in the zolpidem-MR 6.25 group. However, the improvement on WASO, SE and LPS in both studies favored the placebo group.

6 LABELING

Controlled trials supporting safety and efficacy of Ambien CR

: Ambien CR was evaluated in two placebo- controlled studies for the treatment of patients with primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM- IV). Adult outpatients (18- 64 years) with primary insomnia (N= 212) were evaluated in a double- blind, randomized, parallel- group, 3- week trial comparing Ambien CR 12.5 mg and placebo. Ambien CR 12.5 mg was superior to placebo, on objective measures (polysomnography recordings)

sleep induction (by decreasing latency to persistent sleep) during the first 2 nights. ~~and after 2 weeks of treatment. Ambien CR 12.5 mg was also superior to placebo on the patient's global impression regarding the aid to sleep, after the first two nights and after 3 weeks of treatment.~~

Elderly outpatients (= 65 years) with primary insomnia (N= 205) were evaluated in a double- blind, randomized, parallel- group, 3- week trial comparing Ambien CR 6.25 mg and placebo. Ambien CR 6.25 mg was superior to placebo, on objective measures (polysomnography recordings) of

~~Ambien CR 6.25 mg was also superior to placebo on the patient's global impression regarding the aid to sleep, after the first 2 nights and after 3 weeks of treatment.~~

Next- day residual effects:

. In addition, no evidence of next- day residual effects ~~were~~ detected with Ambien CR 12.5 mg and 6.25 mg using self- ratings of sedation.

Rebound effects: In the two placebo- controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of Ambien CR. On the second night, there was no worsening compared to baseline in the Ambien CR group.

APPENDIX

A.1 Exploratory Analyses

As a result of the primary efficacy analysis, it was found that there is evidence that both zolpidem-MR 12.5 mg and zolpidem-MR 6.25 are effective in providing *persistence* in hypnotic effect, by reducing WASO during the first 6 hours after lights-out to patients with primary insomnia. However, this evidence was not supported when completed WASO (WASO during the first 8 hours) was used.

I conducted post-hoc analyses to evaluate the persistence in hypnotic effect of zolpidem-MR by exploring the relationships between the primary efficacy outcome variable and the secondary efficacy variables, as well as exploring the relationship between subjects whose completed WASO decreased (improved) from baseline with subjects whose WASO between hours 1 to hours 6 decreased (improved) from baseline. In these analyses, all continuous outcome variables were dichotomized into "improved" or "no change/did not improve" based on the criteria of improvement for each outcome variables. For example, subject who had a decrease in completed WASO from baseline is coded as "improved", while subject whose WASO increases or did not change is coded as "no change/did not improve".

The frequency distribution of the new outcome variables are presented in Tables A1 to A3. There is evidence that during the first 2 days or nights, a higher proportion of subjects taking zolpidem-MR considerably improved in the objective and subjective sleep measures (i.e. primary and secondary efficacy variables) than those in the placebo group. In contrast, only objective WASO measured during the first 6 hours after lights out and the Patient's Global Impression score appeared to differ between the treatment groups during days or nights 15 and 16, favoring the zolpidem-MR treated group. A similar conclusion can also be drawn looking at the cumulative distribution of subjects having improvements in the primary efficacy variable and the prioritized secondary variables. The next 6 graphs (Figure 1A – 1F) show on what combination of primary outcome and the prioritized secondary objective/subjective measures each subject improved using the ITT population. Because the results in Study EFC4529 with respect to the inclusion of subjects with major protocol deviations did not differ from the results when these subjects were excluded, all succeeding analyses were done based on the ITT population.

Table A1: Frequency Distribution of the Number of Improved Subjects according to the outcome variables (Study EFC4529) – ITT Population

	Placebo		Zolpidem	
	N=110	%	N=102	%
N2/D2				
Completed WASO	70	64%	91	89%
WASO H1 to H6	76	69%	95	93%
Sleep Efficiency	84	76%	94	92%
Latency to Persistent Sleep	75	68%	91	89%
Quality of Sleep	54	49%	86	84%
PGI	53	48%	74	73%
Refreshing Quality of Sleep	51	46%	74	73%
Subjective WASO	56	51%	82	80%
Subjective TST	70	64%	86	84%
Subjective SOL	65	59%	87	85%
Number of Awakenings	63	57%	79	77%
Subjective Number of Awakenings	65	59%	86	84%
Difficulty in Activities	42	38%	51	50%
N16/D16				
Completed WASO	75	68%	74	73%
WASO H1 to H6	76	69%	89	87%
Sleep Efficiency	79	72%	75	74%
Latency to Persistent Sleep	78	71%	79	77%
Quality of Sleep	59	54%	62	61%
PGI	38	35%	79	77%
Refreshing Quality of Sleep	53	48%	62	61%
Subjective WASO	57	52%	63	62%
Subjective TST	71	65%	77	75%
Subjective SOL	69	63%	74	73%
Number of Awakenings	58	53%	75	74%
Subjective Number of Awakenings	66	60%	74	73%
Difficulty in Activities	53	48%	61	60%

Table A2: Frequency Distribution of the Number of Improved Subjects according to the outcome variables (Study EFC4529) – ITT Population with NO MAJOR DEVIATIONS

	Placebo		Zolpidem	
	N=89	%	N=93	%
N2/D2				
Completed WASO	58	65%	85	91%
WASO H1 to H6	62	70%	87	94%
Sleep Efficiency	65	73%	87	94%
Latency to Persistent Sleep	58	65%	83	89%
Quality of Sleep	48	54%	78	84%
PGI	45	51%	70	75%
Refreshing Quality of Sleep	42	47%	67	72%
Subjective WASO	44	49%	76	82%
Subjective TST	59	66%	77	83%
Subjective SOL	48	54%	78	84%
Number of Awakenings	52	58%	77	83%
Subjective Number of Awakenings	65	59%	86	84%
Difficulty in Activities	34	38%	48	52%
N16/D16				
Completed WASO	61	69%	71	72%
WASO H1 to H6	64	72%	81	87%
Sleep Efficiency	61	69%	72	77%
Latency to Persistent Sleep	60	67%	73	78%
Quality of Sleep	49	55%	56	60%
PGI	32	36%	72	77%
Refreshing Quality of Sleep	43	48%	57	61%
Subjective WASO	45	51%	57	61%
Subjective TST	59	66%	69	74%
Subjective SOL	53	60%	69	74%
Number of Awakenings	46	52%	71	76%
Subjective Number of Awakenings	55	62%	68	73%
Difficulty in Activities	44	49%	56	60%

Table A3: Frequency Distribution of the Number of Improved Subjects according to the outcome variables – Study EFC4530

	Placebo		Zolpidem	
	N=106	%	N=99	%
N2/D2				
WASO H1 to H6	62	58%	93	94%
Completed WASO	55	52%	85	86%
Sleep Efficiency	65	61%	92	93%
Latency to Persistent Sleep	65	61%	87	88%
Quality of Sleep	54	51%	68	69%
PGI	57	54%	68	69%
Refreshing Quality of Sleep	52	49%	63	64%
Subjective WASO	48	45%	68	69%
Subjective TST	68	64%	78	79%
Subjective SOL	64	60%	78	79%
Number of Awakenings	62	58%	63	64%
Subjective Number of Awakenings	62	58%	65	66%
Difficulty in Activities	48	45%	37	37%
N16/D16				
WASO H1 to H6	65	61%	75	76%
Completed WASO	62	58%	62	63%
Sleep Efficiency	69	65%	68	69%
Latency to Persistent Sleep	66	62%	75	76%
Quality of Sleep	58	55%	48	48%
PGI	51	48%	63	64%
Refreshing Quality of Sleep	46	43%	53	54%
Subjective WASO	46	43%	53	54%
Subjective TST	70	66%	68	69%
Subjective SOL	72	68%	69	70%
Number of Awakenings	62	58%	48	48%
Subjective Number of Awakenings	72	68%	66	67%
Difficulty in Activities	40	38%	36	36%

In study EFC4529, 89% of subjects in the zolpidem-MR group during the first 2 nights had a reduction in the objective WASO compared to 64% in the placebo group (Figure 1A). All 89% of these subjects in the zolpidem-MR group also had improved sleep efficiency (SE) compared to 63% who had both improved objective WASO and sleep efficiency. Going further down the list, 81% of subjects in the zolpidem-MR group had improved WASO, SE and latency to persistent sleep (LPS) compared to only 42% in the placebo group. Moreover, 71% of subjects in the zolpidem-MR group had improved WASO, SE, LPS, and quality of sleep compared to only a quarter (25%) in the placebo group. This continues on with the rest of the secondary outcome variables. The main result here suggests that at Nights 1 and 2, there is strong evidence of effectiveness of zolpidem-MR in providing immediate hypnotic relief, not only by reducing the objective WASO, but also improving the sleep efficiency, sleep induction (LPS), the quality of sleep, patient's global impression (PGI) score, as well as other subjective and objective sleep measures (Figure 1A, and 1D). The evidence was clearly reflected by the proportion of subjects whose WASO had improved and also had improved quality of sleep. Based on the results, only 18% in the zolpidem-MR group who improved in WASO did not improve in quality of sleep compared to 39% in the placebo group. This result is completely different during the last two nights of treatment (Days 15 and 16), regardless of whether WASO was measured during the first 6 hours or during the first 8 hours. Although a substantial proportion of subjects in the zolpidem-MR group improved in WASO during the first 6 hours compared to the placebo group, and the difference is slightly lower when WASO during the first 8 hours is used instead, there is evidence that the improvement in WASO, sleep efficiency or latency did not carry over to the improvement in the quality of sleep among these subjects. From Figures 1B, 1C, 1E and 1F, there is evidence of considerable reduction in the proportion of subjects who had improved quality of sleep from those who had improved WASO, regardless of the duration of WASO measured. There is at least 33% in the zolpidem-MR group and 35% in the placebo group who did not have improved quality of sleep in Study EFC4529 using completed WASO, and at least 44% and 38% when WASO during the first 6 hours is used, respectively. Similarly in Study EFC4530, at least 33% and 44% in the zolpidem-MR and at least 31% and 34% in the placebo group, completed WASO and WASO H1 to H6, respectively did not improve in their quality of sleep.

APPEARS THIS WAY ON ORIGINAL

Figure 1A:

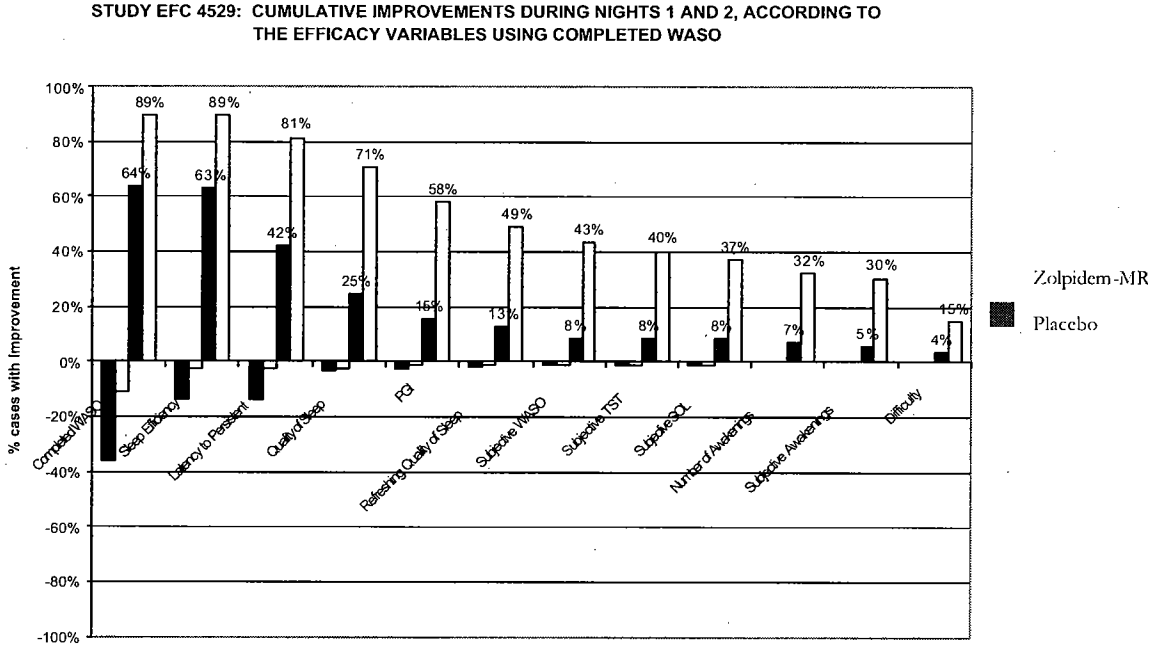


Figure 1B:

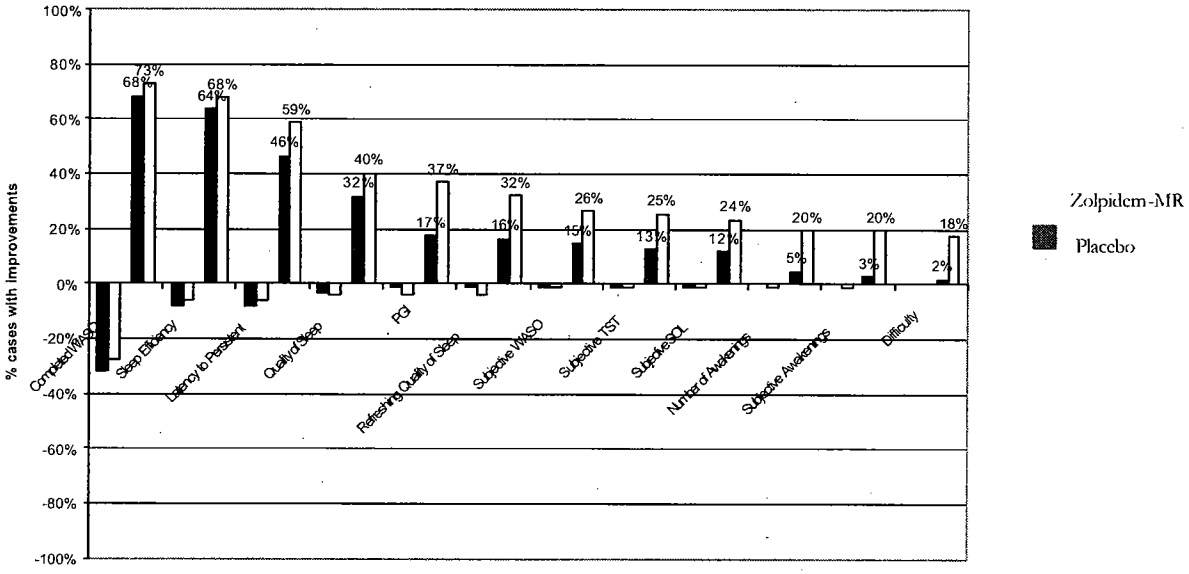


Figure 1C:

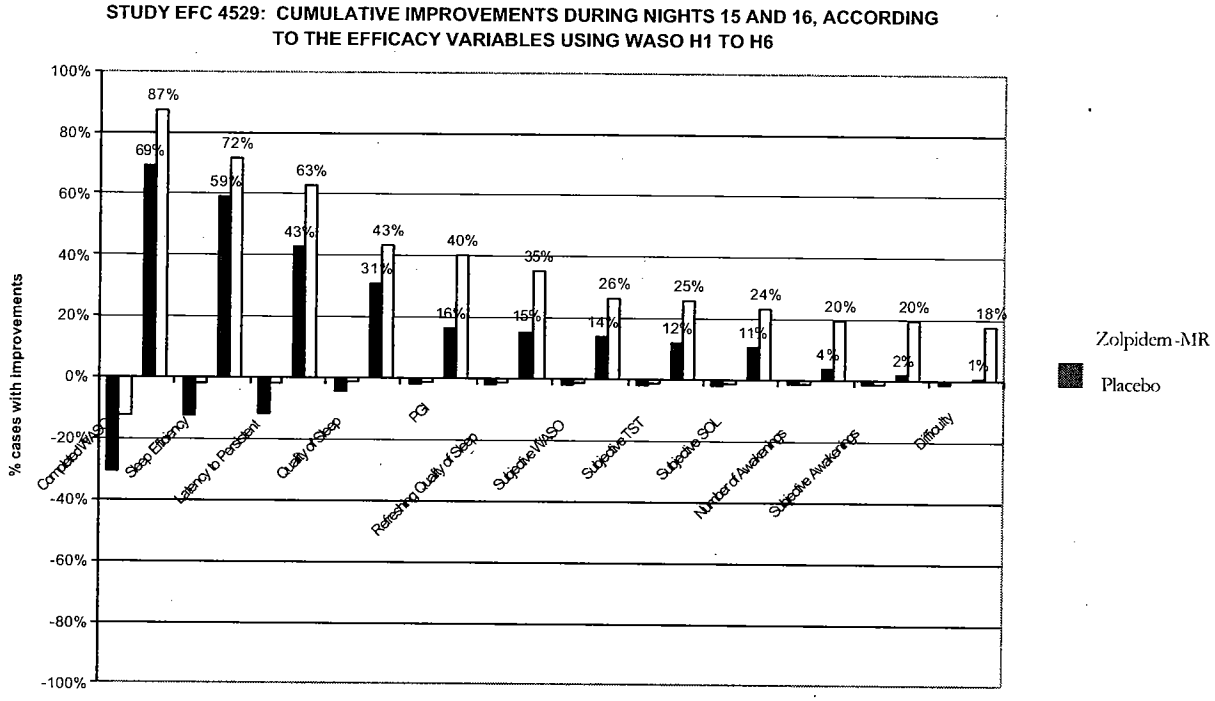


Figure 1D:

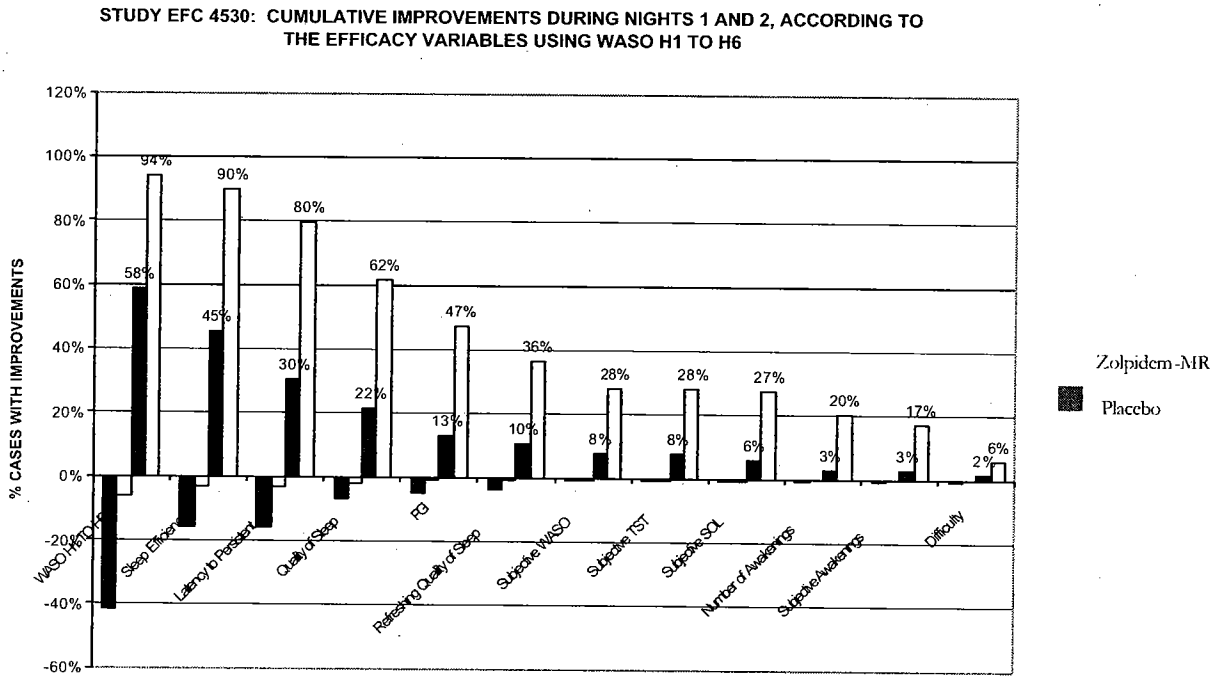


Figure 1E:

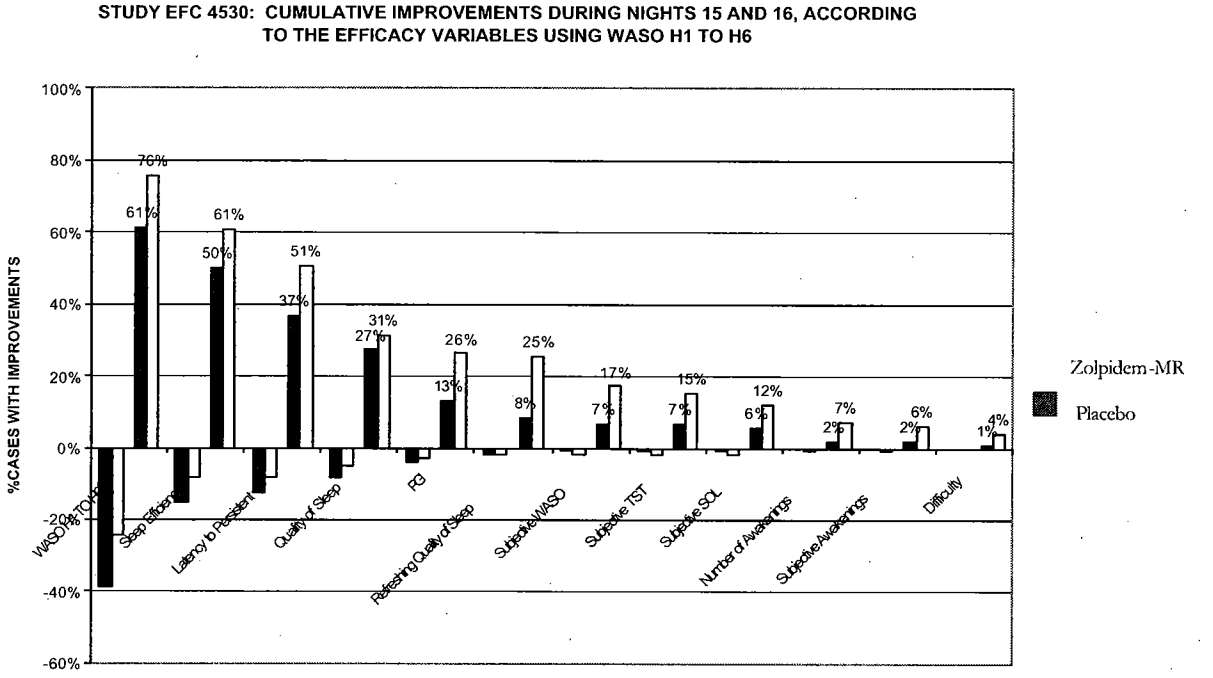
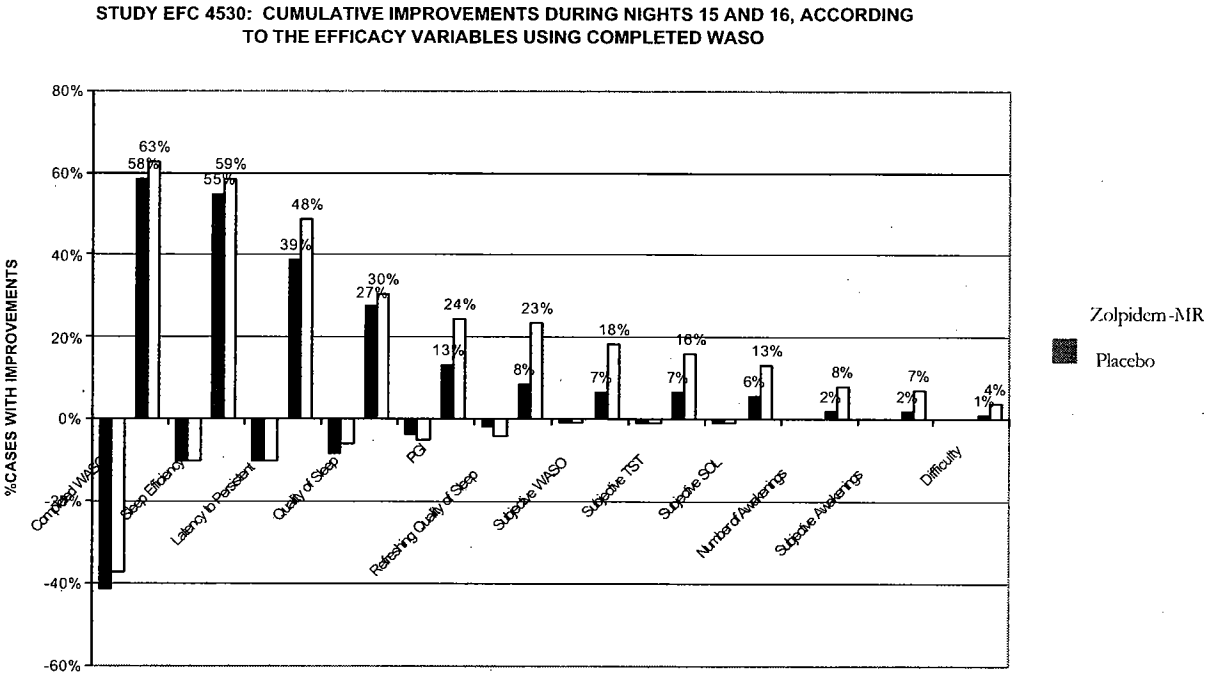


Figure 1F:



Additional evidence that zolpidem-MR may not be effective in providing persistence hypnotic effect is when I analyzed subset of population who showed improvement when WASO is measured both during the first 6 hours and during the first 8 hours. In study EFC4529, out of 110 subjects in the placebo group, only 66 subjects' WASO improved when measured during the first 6 hours and during first 8 hours, as opposed to 76 when WASO during the first 6 hours was used. Meanwhile, of the 102 subjects in the zolpidem-MR group, 73 out of the 89 subjects who improved based on the WASO during the first 6 hours also improved when completed WASO was measured. This implies a larger discordant pair in the zolpidem-MR group than the placebo group. Similarly in Study EFC4530, a larger proportion of subjects in the zolpidem-MR group were discordant in terms of improvements compared to the placebo. Analyzing only subjects who improved using both measurements yield non-significant difference between the zolpidem-MR and the placebo based on one-way Analysis of Variance in Study EFC4529, and ANCOVA in Study EF4530 (Table A4). No apparent differences existed between using all subjects and the subsets during Nights 1 and 2, in both studies.

Table A4: Results (p-values) on Subset of Patients who improved using WASO measurements taken during the first 6 hours or during the first 8 hours, at Nights 15/16

	N1/N2		N15/N16	
	Original	Subset	Original	Subset
EFC 4529 (ANOVA)				
Completed WASO	0.0002	0.0009	0.6489	0.3743
WASO H1 to H6	0.0005	0.0006	0.0293	0.1417
EFC 4530 (ANCOVA)				
Completed WASO	<0.0001	<0.0001	0.1485	0.1916
WASO H1 to H6	<0.0001	<0.0001	0.0042	0.0363

Based on these findings, there is evidence that zolpidem-MR is effective in providing immediate hypnotic to patients with primary insomnia. However, the evidence that zolpidem-MR is effective in providing persistence hypnotic effect is hard to justify even when the primary outcome measure is significant.

A.2 Next-Day Residual Effects

Three additional pharmacodynamic studies were conducted to evaluate the residual psychomotor and cognitive performances 8 hours after post-dosing (Table A1).

Table B1: Pharmacodynamic studies that assessed potential residual effects of zolpidem-MR

	Healthy Young Subjects	Healthy Elderly Subjects	8 hours Postdosing	9 hours Postdosing	Zolpidem-MR 12.5 mg	Zolpidem-MR 6.25 mg
PDY4054	X		X	X	X	
PDY5035		X	X		X	X
PDY5036	X		X		X	

The first study (PD4054) was a Phase I, single center, double-blind, placebo-controlled, 10-way cross-over study comparing the pharmacodynamic effects of eight galenic formulations of zolpidem-MR versus current marketed immediate release (IR) form of zolpidem, in 36 healthy subjects (Table B2). In this study, next-day residual effect was evaluated as part of the secondary objectives, and is measured by as measured by Critical Flicker Fusion (CFF), Choice Reaction Time (CRD), Compensatory Tracking Task (CTT), immediate Word Recall (WRi), delayed Word Recall (WRd), and Digit Symbol Substitution Test (DSST)..

Table B2: Combination of IR and PR considered in the MR-formulations used in this study

Immediate Release (dose released[1] in 30 min.)	Prolonged Release (dose released[1] 30 min.- 4 hours)		
		5 mg	
7.5 mg		E	

Table B3: Summary of the content-release relationship for the formulations used in the study, compared with the marketed tablet

	A	B	C	D	E	F	G	H	Stilnox
Total Dose (mg)			12.5		12.5		12.5		10
Drug content of layer 1									NA
Drug content of layer 2									NA
Dose released within 30 min.					7.5				10
Dose released 30 min.-4 h					5.0				NA

NA = Not Applicable

The residual psychomotor and cognitive endpoints were summarized by treatment and night hours, and were analyzed using a linear mixed effects model:

Y=Sequence + Subject(Sequence) + Period + Treatment + Error

with fixed term for sequence, period, and treatment, and random term for subject within sequence, using SAS Proc MIXED procedure.

Pairwise comparisons versus placebo were performed using linear contrasts: estimate and 95% CIs for difference between the active treatments and the placebo, and these were all calculated within mixed model framework. Each test of the battery was considered separately in an exploratory manner. Statistically significant differences were interpreted using the 95% CI and according to their clinical relevance.

According to the applicant, the results of the psychometric and cognitive tests indicated that Formulations F, G, and H induced impairment of psychometric and cognitive function 8 – 9 hours post-dosing. Formulations B, C, and D had some residual effects and no evidence of residual effects (in terms of a statistically significant results) was observed for Formulations A and E. Overall, the pharmacodynamic results indicate that, of the 8 galenic formulations of zolpidem-MR tested in the study, formulation E (12.5 mg dosage) produces a more prolonged duration of activity than Stilnox with no residual effects (see Table B4 – A5).

Table B4: Summary of mean (SEM) psychomotor and cognitive test results for formulations A to H, versus placebo and Stilnox

	Placebo	Stilnox	A	B	C	D
Results 8h Post-Dose						
CFF (Hz)	30.88 (0.47)	30.74 (0.48)	30.86 (0.42)	30.63 (0.41)	30.52 (0.50)	30.70 (0.43)
CTTd (pixels)	19.88 (1.76)	20.45 (1.63)	20.33 (1.85)	19.48 (1.24)	25.02 (4.31)	23.08 (1.77)
CTT t (ms)	508.04 (19.55)	516.26 (21.06)	515.88 (19.29)	516.91 (21.17)	572.23 (42.86)	557.73 (25.36)
DSST No. completed	77.41 (2.99)	78.86 (2.65)	78.57 (2.84)	76.24 (2.63)	73.40 (2.95)	76.37 (2.68)
CRT Motor reaction time (ms)	215.25 (9.51)	221.58 (11.36)	220.12 (11.03)	213.67 (11.66)	209.68 (11.54)	223.48 (10.13)
CRT Recognition reaction time (ms)	390.32 (9.85)	396.05 (9.90)	392.45 (10.51)	404.28 (12.38)	414.50 (14.09)	415.93 (16.80)
CRT Total reaction time (ms)	605.58 (17.69)	617.64 (17.87)	612.57 (16.95)	617.96 (19.49)	624.18 (19.67)	639.42 (23.06)
WRd (n)	11.09 (0.91)	10.11 (0.80)	11.03 (0.86)	10.47 (0.88)	9.91 (0.77)	10.03 (0.76)
WRi (n)	15.26 (0.65)	14.83 (0.67)	15.77 (0.64)	15.00 (0.68)	14.57 (0.63)	15.06 (0.61)
Results 9h post-dose						
CFF (Hz)	30.74 (0.43)	30.70 (0.48)	30.63 (0.45)	30.77 (0.41)	30.35 (0.35)	30.71 (0.42)
CTTd (pixels)	17.71 (1.23)	18.99 (1.65)	17.28 (0.92)	17.44 (0.92)	18.06 (1.24)	19.13 (1.04)
CTT t (ms)	479.51 (14.61)	509.22 (19.93)	480.33 (12.54)	490.96 (14.82)	491.74 (15.26)	510.69 (17.78)
DSST No. completed	85.53 (2.83)	83.71 (2.86)	85.23 (2.74)	84.03 (3.00)	83.20 (3.13)	84.09 (2.61)
CRT Motor reaction time (ms)	213.37 (9.19)	204.09 (9.04)	207.80 (10.15)	207.51 (12.23)	199.58 (9.56)	208.27 (9.39)
CRT Recognition reaction time (ms)	379.33 (9.93)	394.42 (11.42)	369.11 (8.64)	399.79 (11.80)	394.21 (12.81)	381.85 (9.44)
CRT Total reaction time (ms)	592.71 (17.16)	598.51 (17.23)	576.91 (15.25)	607.31 (19.44)	593.79 (17.36)	590.12 (15.44)

PGM= /biom/clinic/SL800750/PDY4054/CSR/damon/program/instpsy4.sas Out= PDY4054/CSR/damon/Instpsy4 (13JUN2002 - 16:21)
Ref.: Appendices 16.2.6.2.1.1.1 – 16.2.6.2.1.1.6

	Placebo	Stilnox	E	F	G	H
Results 8h Post-Dose						
CFF (Hz)	30.88 (0.47)	30.74 (0.48)	30.53 (0.46)	30.82 (0.43)	30.84 (0.49)	30.73 (0.49)
CTTd (pixels)	19.88 (1.76)	20.45 (1.63)	19.88 (1.50)	25.18 (2.49)	22.17 (1.64)	22.11 (1.78)
CTTt (ms)	508.04 (19.55)	516.26 (21.06)	519.56 (20.83)	568.76 (35.15)	570.09 (35.91)	542.41 (25.86)
DSST No. competed	77.41 (2.99)	78.86 (2.65)	78.44 (2.81)	74.85 (2.61)	76.12 (2.60)	75.06 (3.02)
CRT Motor reaction time (ms)	215.25 (9.51)	221.58 (11.36)	224.84 (11.76)	234.81 (12.25)	222.87 (10.41)	230.73 (12.22)
CRT Recognition reaction time (ms)	390.32 (9.85)	396.05 (9.90)	394.72 (9.32)	408.61 (16.49)	397.64 (12.80)	402.14 (14.47)
CRT Total reaction time (ms)	605.58 (17.69)	617.64 (17.87)	619.56 (17.98)	643.43 (23.88)	620.51 (20.87)	632.88 (23.42)
WRd (n)	11.09 (0.91)	10.11 (0.80)	10.21 (0.80)	9.74 (0.77)	9.41 (0.84)	9.39 (0.87)
WRi (n) run	15.26 (0.65)	14.83 (0.67)	14.91 (0.62)	14.71 (0.60)	14.65 (0.64)	14.21 (0.62)
Results 9h post-dose						
CFF (Hz)	30.74 (0.43)	30.70 (0.48)	30.46 (0.41)	30.58 (0.34)	30.92 (0.48)	30.94 (0.46)
CTTd (pixels)	17.71 (1.23)	18.99 (1.65)	18.42 (1.33)	20.26 (1.55)	19.08 (1.52)	18.88 (1.21)
CTTt (ms)	479.51 (14.61)	509.22 (19.93)	496.07 (22.78)	508.92 (18.37)	506.12 (18.12)	519.90 (20.56)
DSST No. competed	85.53 (2.83)	83.71 (2.86)	83.32 (2.92)	81.32 (2.65)	81.35 (2.81)	83.94 (3.10)
CRT Motor reaction time (ms)	213.37 (9.19)	204.09 (9.04)	210.97 (9.96)	218.58 (11.72)	215.96 (8.84)	212.25 (10.79)
CRT Recognition reaction time (ms)	379.33 (9.93)	394.42 (11.42)	373.99 (8.19)	380.31 (9.60)	376.90 (9.83)	380.71 (10.52)
CRT Total reaction time (ms)	592.71 (17.16)	598.51 (17.23)	584.97 (15.92)	598.89 (16.76)	592.87 (16.01)	592.97 (19.11)

PGM= /biom/clinic/SL800750/PDY4054/CSR/damon/program/instpsy4.sas Out= PDY4054/CSR/damon/Instpsy4 (13JUN2002 - 16:21)
Ref.: Appendices 16.2.6.2.1.1.1 – 16.2.6.2.1.1.6

Table B5: Summary of the statistical analyses of the psychomotor test results at 8 hours and 9 hours post dosing.

	A	B	C	D	E	F	G	H	Stilnox
CFF (Hz)	-	-	-	-	-	-	-	-	-
CTTd (pixels)	-	-	+ at 8h	-	-	+ at 8h ↓ at 9h	-	+ at 9h	-
CTTt (ms)	-	-	+ at 8h	+ at 9h	-	↓ at 8h	↓ at 8h	+ at 9h	+ at 9h
DSST No. completed	-	-	+ at 8h	-	-	↓ at 9h	↓ at 9h	-	-
CRT – Motor reaction time (ms)	-	-	-	-	-	+ at 8h	-	+ at 8h	-
CRT – Recognition reaction time (ms)	-	+ at 9h	-	+ at 8h	-	-	-	-	-
WRd* (n)	-	-	-	-	-	↓ at 8h	↓ at 8h	↓ at 8h	-
WRi* (n)	-	-	-	-	-	-	-	↓ at 8h	-

* Not performed 9 hours post-dose
↓ : test statistically different from placebo
- : test not statistically different from placebo
Ref.: Appendix 16.2.6.2.1.2

The second study (PDY5035) was a Phase I, single center, double-blind, randomized, 4-way cross-over, placebo-controlled investigation of the psychomotor and cognitive residual effects of single oral doses of zolpidem-MR 6.25 mg, zolpidem-MR 12.5 mg and flurazepam 30 mg in comparison with placebo in 24 healthy elderly volunteers (sample size of 24 was calculated based on the Critical Flicker Fusion test from PDY4054, assuming SD_{within} equal to 1.5). In this study, the primary objective was to assess the residual and psychomotor and cognitive effects 8 hours after a single oral dose of zolpidem-MR 12.5 and zolpidem-MR 6.25 mg in comparison with placebo, as measured by Critical Flicker Fusion (CFF), Choice Reaction Time (CRD), Compensatory Tracking Task (CTT), immediate Word Recall (WRi), delayed Word Recall (WRd), and Digit Symbol Substitution Test (DSST). The residual psychomotor and cognitive endpoints were summarized by treatment and night hours, and were analyzed using a linear mixed effects model:

$$Y=\text{Sequence} + \text{Subject(Sequence)} + \text{Period} + \text{Treatment} + \text{Error}$$

with fixed term for sequence, period, and treatment, and random term for subject within sequence, using SAS Proc MIXED procedure.

Pairwise comparisons versus placebo were performed using linear contrasts: estimate and 95% CIs for difference between the active treatments and the placebo, and these were all calculated within mixed model framework. Each test of the battery was considered separately in an exploratory manner. Statistically significant differences were interpreted using the 95% CI and according to their clinical relevance.

According to the applicant, the psychomotor and cognitive test results confirmed the residual effect of flurazepam used as a positive control to validate the test battery. Furthermore, the results of these objective tests demonstrated that zolpidem-MR at 6.25 mg and 12.5 mg dose has no residual effect 8 hours post-dosing in elderly subjects. Pairwise comparisons between both doses of zolpidem-MR and placebo indicated no statistically significant differences on CFF values, CRT recognition time, motor reaction time and total reaction time, immediate and delayed word recall, CTT mean deviation and time reaction, and DSST. This suggests that zolpidem-MR 6.25 or 12.5 mg has no residual effects on the integrative capacity of the central nervous system, sensorimotor performance, immediate and delayed memory, or psychomotor performance (see Table B6 and A7).

Table B6: Summary of psychomotor and cognitive test results (PDY 5035)

Parameter	Statistics	Placebo (N=23)	Zolpidem-MR 6.25 mg (N=23)	Zolpidem-MR 12.5 mg (N=23)	Flurazepam 30 mg (N=23)
CFF (Hz)	Mean (SEM)	28.03 (0.59)	28.22 (0.54)	27.60 (0.55)	27.29 (0.46) *
	Min - Max	20.62 - 33.12	23.37 - 32.37	20.50 - 32.62	24.00 - 31.00
CRT - Recognition reaction time (ms)	Mean (SEM)	524.13 (16.30)	513.68 (17.86)	535.50 (19.43)	547.93 (19.42)
	Min - Max	378.64 - 640.13	338.46 - 683.86	382.55 - 771.86	357.84 - 708.40
CRT - Motor reaction time (ms)	Mean (SEM)	318.15 (14.91)	327.48 (16.48)	315.18 (17.11)	342.54 (19.44)
	Min - Max	174.03 - 426.10	174.03 - 483.34	177.58 - 500.05	211.71 - 575.25
CRT - Total reaction time (ms)	Mean (SEM)	842.28 (22.68)	841.16 (24.72)	850.68 (25.36)	890.48 (28.35)
	Min - Max	662.35 - 998.51	625.91 - 1000.64	625.55 - 1030.51	625.38 - 1184.10
Immediate word recall	Mean (SEM)	9.2 (0.5)	8.8 (0.6)	8.5 (0.7)	6.4 (0.4)
	Min - Max	5 - 13	5 - 14	3 - 14	2 - 11
Delayed word recall	Mean (SEM)	6.0 (0.7)	5.9 (0.6)	4.9 (0.8)	3.0 (0.5)
	Min - Max	2 - 12	1 - 13	0 - 13	0 - 9
CTT - Mean deviation (pixels)	Mean (SEM)	31.09 (4.07)	28.42 (3.10)	35.17 (5.25)	38.56 (6.06)
	Min - Max	12.47 - 93.28	11.77 - 61.56	15.13 - 103.35	14.34 - 131.86
CTT - Mean response time (ms)	Mean (SEM)	655.49 (30.95)	634.80 (27.00)	697.46 (53.01)	768.11 (60.48)
	Min - Max	453.00 - 1033.43	454.92 - 929.70	446.97 - 1360.22	466.68 - 1433.62
DSST	Mean (SEM)	28.5 (1.9)	29.2 (1.6)	29.3 (1.7)	26.6 (1.5)
	Min - Max	17 - 47	11 - 43	12 - 45	15 - 41

Table B7: Summary of the statistical analysis of the psychomotor and cognitive test results.

Parameter	Estimate [95% CI] and p-value		
	Zolpidem-MR 6.25 mg vs Placebo	Zolpidem-MR 12.5 mg vs Placebo	Flurazepam 30 mg vs Placebo
CFF (Hz)	0.20 [-0.38 ; 0.77] p=0.4970	-0.44 [-1.02 ; 0.14] p=0.1312	-1.01 [-1.59 ; -0.42] p=0.0011
CRT - Recognition reaction time (ms)	-10.60 [-36.75 ; 15.56] p=0.4212	11.18 [-14.97 ; 37.33] p=0.3962	24.05 [-2.10 ; 50.20] p=0.0709
CRT - Motor reaction time (ms)	9.16 [-12.51 ; 30.82] p=0.4015	-2.22 [-23.89 ; 19.44] p=0.8383	25.03 [3.36 ; 46.69] p=0.0243
CRT - Total reaction time (ms)	-1.44 [-35.13 ; 32.26] p=0.9322	8.96 [-24.74 ; 42.65] p=0.5972	49.07 [15.38 ; 82.77] p=0.0050
Immediate word recall	-0.34 [-1.47 ; 0.78] p=0.5424	-0.68 [-1.80 ; 0.45] p=0.2328	-2.76 [-3.88 ; -1.63] p=0.0001
Delayed word recall	-0.08 [-1.29 ; 1.13] p=0.8935	-1.05 [-2.26 ; 0.16] p=0.0876	-2.94 [-4.15 ; -1.73] p=0.0001
CTT - Mean deviation (pixels)	-2.55 [-10.53 ; 5.43] p=0.5260	4.20 [-3.78 ; 12.18] p=0.2974	7.28 [-0.70 ; 15.26] p=0.0732
CTT - Mean response time (ms)	-19.59 [-113.56 ; 74.39] p=0.6785	43.80 [-50.17 ; 137.78] p=0.3552	112.46 [18.49 ; 206.43] p=0.0198
DSST	0.68 [-1.24 ; 2.61] p=0.4817	0.73 [-1.20 ; 2.65] p=0.4519	-1.90 [-3.83 ; 0.02] p=0.0526

Lastly, the third study (PDY5036) was a Phase I, single center, double-blind, randomized, 3-way cross-over, placebo-controlled investigation of the psychomotor and cognitive residual effects of single oral doses of zolpidem-MR 12.5 mg and flurazepam 30 mg in comparison with placebo in 24 healthy young volunteers (sample size of 18 was calculated based on the Critical Flicker Fusion test from PDY4054, assuming SD_{within} equal to 1.5). In this study similar to PDY5035, the primary objective was to assess the residual and psychomotor and cognitive effects 8 hours after a single oral dose of zolpidem-MR 12.5 mg in comparison with placebo, as measured by Critical Flicker Fusion (CFF), Choice Reaction Time (CRD), Compensatory Tracking Task (CTT), immediate Word Recall (WRi), delayed Word Recall (WRd), and Digit Symbol Substitution Test (DSST). The residual psychomotor and cognitive endpoints were summarized by treatment and night hours, and were analyzed using a linear mixed effects model:

$$Y=\text{Sequence} + \text{Subject(Sequence)} + \text{Period} + \text{Treatment} + \text{Error}$$

with fixed term for sequence, period, and treatment, and random term for subject within sequence, using SAS Proc MIXED procedure.

Pairwise comparisons versus placebo were performed using linear contrasts: estimate and 95% CIs for difference between the active treatments and the placebo, and these were all calculated within mixed model framework. Each test of the battery was considered separately in an exploratory manner. Statistically significant differences were interpreted using the 95% CI and according to their clinical relevance.

According to the applicant, the psychomotor and cognitive test results confirmed the residual effect of flurazepam used as a positive control to validate the test battery. Furthermore, the results of these objective tests demonstrated that a single dose of zolpidem-MR 12.5 mg has no residual effect 8 hours post-dosing. Pairwise comparisons between both doses of zolpidem-MR and placebo indicated no statistically significant differences on CFF values, CRT recognition time, motor reaction time and total reaction time, immediate and delayed word recall, CTT mean deviation and

time reaction, and DSST. This suggests that zolpidem-MR 12.5 mg has no residual effects on the integrative capacity of the central nervous system, sensorimotor performance, immediate and delayed memory, or psychomotor performance except the CTT time reaction (see Table B8 to A9).

Table B8: Summary of psychomotor and cognitive test results (PDY 5036)

Parameter	Statistics	Placebo (N=18)	Zolpidem-MR 12.5 mg (N=18)	Flurazepam 30 mg (N=18)
CFF (Hz)	Mean (SEM)	29.12 (0.46)	28.97 (0.56)	28.22 (0.61)
	Min - Max	24.62 - 32.25	25.00 - 34.37	22.87 - 34.12
CRT - Recognition reaction time (ms)	Mean (SEM)	372.22 (9.33)	377.44 (7.82)	393.88 (9.80)
	Min - Max	328.15 - 481.74	314.29 - 424.50	327.26 - 476.77
CRT - Motor reaction time (ms)	Mean (SEM)	246.65 (13.97)	257.52 (12.83)	268.59 (13.97)
	Min - Max	151.98 - 383.61	160.34 - 366.91	191.27 - 370.28
CRT - Total reaction time (ms)	Mean (SEM)	618.87 (19.14)	634.97 (15.73)	662.47 (16.86)
	Min - Max	493.66 - 865.37	546.81 - 785.19	572.76 - 796.21
Immediate word recall	Mean (SEM)	13.2 (0.8)	12.7 (0.6)	10.7 (0.7)
	Min - Max	7 - 19	9 - 18	4 - 15
Delayed word recall	Mean (SEM)	10.3 (0.8)	8.9 (0.8)	5.9 (0.8)
	Min - Max	2 - 16	3 - 17	0 - 13
CTT - Mean deviation (pixels)	Mean (SEM)	14.51 (0.63)	16.06 (0.74)	17.30 (1.06)
	Min - Max	10.9 - 20.4	11.9 - 22.3	11.7 - 28.8
CTT - Mean response time (ms)	Mean (SEM)	469.5 (13.4)	519.1 (19.8)	565.4 (21.5)
	Min - Max	379 - 572	372 - 703	420 - 767
DSST	Mean (SEM)	63.6 (3.9)	63.7 (3.2)	59.7 (3.2)
	Min - Max	42 - 100	45 - 92	38 - 87
LSEQ - Ease of getting to sleep	Mean (SEM)	41.1 (2.5)	52.7 (2.2)	52.1 (2.6)
	Min - Max	12 - 53	38 - 74	35 - 76
LSEQ - Quality of sleep	Mean (SEM)	36.5 (3.1)	50.5 (3.3)	56.8 (3.4)
	Min - Max	12 - 53	21 - 80	39 - 87
LSEQ - Awakening from sleep	Mean (SEM)	48.3 (1.5)	46.4 (1.4)	42.7 (2.6)
	Min - Max	36 - 63	36 - 56	18 - 61
LSEQ - Behaviour following awakening	Mean (SEM)	44.6 (1.4)	43.1 (1.5)	38.1 (2.5)
	Min - Max	32 - 58	29 - 54	14 - 55
BOND & LADER - Alertness	Mean (SEM)	298.1 (22.0)	309.7 (18.2)	339.7 (17.5)
	Min - Max	80 - 400	93 - 381	144 - 431
BOND & LADER - Contentedness	Mean (SEM)	134.9 (12.6)	122.7 (11.9)	139.7 (11.7)
	Min - Max	31 - 209	26 - 180	15 - 189
BOND & LADER - Calmness	Mean (SEM)	53.1 (5.8)	44.6 (4.6)	45.7 (4.7)
	Min - Max	7 - 88	9 - 70	3 – 65

pgm=SL80075023/PDY5036/CSR/BS/PGM_RPT/t1626.sas out=OUTPUT/t1626st.lst (11JUL2003 - 8:59)

Ref: Appendices 16.2.6.1.1.1, 16.2.6.1.2.1, 16.2.6.1.3.1, 16.2.6.1.4.1, 16.2.6.1.5.1, 16.2.6.1.6.1, and 16.2.6.1.7.1

APPEARS THIS WAY
ON ORIGINAL

Table B9: Summary of the statistical analysis of the psychomotor and cognitive test results.

Parameter	Estimate [95% CI] and p-value	
	Zolpidem-MR 12.5 mg vs Placebo	**Flurazepam 30 mg vs Placebo**
CFF (Hz)	-0.15 [-0.77 ; 0.48] p=0.6375	-0.90 [-1.52 ; -0.27] p=0.0066
CRT - Recognition reaction time (ms)	5.22 [-8.56 ; 19.01] p=0.4458	21.66 [7.87 ; 35.44] p=0.0031
CRT - Motor reaction time (ms)	10.87 [-6.01 ; 27.76] p=0.1989	21.94 [5.06 ; 38.83] p=0.0125
CRT - Total reaction time (ms)	16.10 [-8.03 ; 40.23] p=0.1837	43.60 [19.47 ; 67.73] p=0.0009
Immediate word recall	-0.50 [-2.17 ; 1.17] p=0.5455	-2.50 [-4.17 ; -0.83] p=0.0045
Delayed word recall	-1.39 [-3.28 ; 0.51] p=0.1451	-4.39 [-6.28 ; -2.49] p=0.0001
CTT - Mean deviation (pixels)	1.55 [-0.14 ; 3.24] p=0.0713	2.79 [1.10 ; 4.48] p=0.0020
CTT - Mean response time (ms)	49.56 [12.43 ; 86.68] p=0.0105	95.89 [58.77 ; 133.01] p=0.0001
DSST	0.06 [-4.39 ; 4.50] p=0.9798	-3.94 [-8.39 ; 0.50] p=0.0801
LSEQ - Ease of getting to sleep	11.59 [4.75 ; 18.44] p=0.0016	10.96 [4.12 ; 17.81] p=0.0026
LSEQ - Quality of sleep	13.97 [4.76 ; 23.18] p=0.0041	20.22 [11.01 ; 29.43] p=0.0001
LSEQ - Awakening from sleep	-1.92 [-7.04 ; 3.21] p=0.4520	-5.61 [-10.74 ; -0.48] p=0.0330
LSEQ - Behaviour following awakening	-1.56 [-6.36 ; 3.25] p=0.5140	-6.50 [-11.30 ; -1.70] p=0.0095
BOND & LADER - Alertness	11.64 [-25.54 ; 48.83] p=0.5281	41.68 [4.49 ; 78.86] p=0.0292
BOND & LADER - Contentedness	-12.24 [-27.78 ; 3.30] p=0.1184	4.71 [-10.82 ; 20.25] p=0.5410
BOND & LADER - Calmness	-8.48 [-15.31 ; -1.65] p=0.0166	-7.39 [-14.22 ; -0.56] p=0.0349

pgm=/SL80075023/PDY5036/CSR/BS/PGM_RPT_t1626.sas out=OUTPUT/t1626sa.lst (11JUL2003 - 8:59)

Ref: Appendices 16.2.6.1.1.3, 16.2.6.1.2.3, 16.2.6.1.3.3, 16.2.6.1.4.3, 16.2.6.1.5.3, 16.2.6.1.6.3, and 16.2.6.1.7.3

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joan Buenconsejo
3/3/05 04:04:01 PM
BIOMETRICS

Thomas Permutt
3/3/05 04:21:44 PM
BIOMETRICS
concur

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling