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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00296790
		Study Code:	PM_L_0167
Generic drug name:	Zolpidem Tartrate	**Date:**	11/Oct/2007

Title of the study: A Comparison of Zolpidem Tartrate Extended-Release vs. Placebo in the Treatment of Insomnia Associated with Generalized Anxiety Disorder (GAD) when Used Concomitantly with Escitalopram (Study Number PM_L_0167)

Investigator(s): Multicenter

Study center(s): 41 centers in the USA

Publications (reference): None

Study period:

Date first patient enrolled: 14/Feb/2006

Date last patient completed: 11/Jan/2007

Phase of development: Phase IV (Comparison)

Primary Objective: To demonstrate overall improvement of insomnia, as measured by total sleep time (TST), in patients treated with zolpidem tartrate extended-release and escitalopram vs. patients treated with placebo and escitalopram

Secondary Objective: To demonstrate that treating insomnia from the beginning of selective serotonin reuptake inhibitor (SSRI) treatment for anxiety results in improvement in quality of life and potentially greater response to anxiolytic therapy

Quality of Life Measures: Sleep Impact Scale (SIS), Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ), and the Sheehan Disability Scale (SDS)

Health Economics Measures: Healthcare Resource Utilization (HRU) questionnaire

Safety Outcomes: Safety will be assessed by collection of reported adverse events (AEs), routine physical examinations, laboratory assessments, and treatment discontinuation effects

Methodology: Randomized, double-blind, parallel-group, placebo-controlled, 8-week trial of 12.5 mg zolpidem tartrate extended-release in adults with insomnia associated with GAD who are concomitantly being treated with escitalopram

Number of patients: Planned: 260 completed patients required for analysis (374 planned to be randomized)

Randomized: 383

Treated: 381 received at least 1 dose of study treatment

Evaluated:

Efficacy: Intent-to-treat (ITT) Population: 381 patients; Per-protocol (PP) population: 297 patients

Safety: Safety population: 381 patients

Diagnosis and criteria for inclusion: Adults who meet the diagnostic requirements of GAD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and measured by the Mini International Neuro-psychiatric Interview (MINI), and who also score at least 18 on the Hamilton Rating Scale for Anxiety (HAM-A) and experience sleep disturbances at least 3 nights per week for at least 1 month prior to study entry.

Investigational product: Zolpidem tartrate extended-release

Dose: 12.5 mg nightly

Administration: Oral

Duration of treatment: 8 weeks for randomized treatment, with an additional week of escitalopram treatment

Duration of observation: 9 weeks after first dose of study medication

Reference therapy: Placebo

Dose: Matched to active treatment

Administration: Oral

Mandatory concomitant medication: Escitalopram oxalate

Dose: 10 mg daily

Administration: Oral

Criteria for evaluation:

Efficacy: The primary measure of efficacy was patient report of TST per night, measured by the Morning Sleep Questionnaire (MSQ). Secondary measures included patient questionnaire responses about sleep characteristics (MSQ), impact of anxiety on daily functioning (SDS), anxiety symptoms (HAM-A and Beck Anxiety Inventory [BAI]), quality of life (SIS, Q-LES-Q, and MGH-CPFQ), and healthcare resource utilization (HRU). Clinician ratings of severity of mental illness and improvement (Clinical Global Impression [CGI] scale) and patient ratings of response to study medication (Patient Global Impression of Insomnia Treatment [PGI-IT] scale) were also measured. For most efficacy variables, statistical analyses emphasized the change in scores from baseline to the end of randomized treatment (Week 8).

Safety: AEs reported by the patient or noted by the investigator, standard hematology, blood chemistry, urinalysis, vital signs, physical examination, and sleep characteristics (measured by the MSQ) during the follow-up period.

Statistical methods: The primary efficacy analysis used analysis of covariance (ANCOVA) on the ITT population to compare change in TST from baseline to the end of randomized treatment (Week 8) in patients treated with zolpidem tartrate extended-release plus escitalopram vs. placebo plus escitalopram. The ANCOVA model consisted of treatment group and gender as fixed effect terms and baseline TST as the covariate. Alpha level was 0.05.

Secondary efficacy analyses used a similar ANCOVA approach to analyze secondary efficacy variables. Non-parametric tests were used, as applicable. Descriptive statistics were also calculated for all efficacy variables.

Safety analyses were done on all patients who received at least 1 dose of study medication. Adverse events were summarized in frequency tables by treatment group, SOC, and preferred term, and by severity and relationship to study medication. Laboratory safety measures were summarized with descriptive statistics by treatment group and visit, and were also analyzed in shift tables. Possibly clinically significant laboratory values (alert values) were listed by subject. Vital signs were summarized descriptively by treatment group and visit. Normal and abnormal physical examination findings were summarized in frequency tables by treatment group and visit.

Compliance and medication exposure were analyzed descriptively by treatment group. Treatment groups were compared using one-way ANOVA.

Summary:

Efficacy results:

Variable (change from Baseline value to Week 8)	Placebo plus escitalopram (N=190)	Zolpidem tartrate extended-release plus escitalopram (N=191)	p-value for difference in improvement
Change in total sleep time (TST)	68.2 min	106.0 min	<0.0001
Change in sleep onset latency	-26.8 min	-55.1 min	<0.0001
Change in wake time after sleep onset	-28.8 min	-40.7 min	<0.0001
Change in HAM-A anxiety score	-12.5	-13.3	.4095
Change in BAI anxiety score	-14.3	-13.1	.0294

The zolpidem tartrate extended-release/escitalopram treatment group had significantly more improvement in TST and all other sleep characteristics than patients treated with placebo/escitalopram; these treatment group differences were statistically significant at all visits during the 8 weeks of treatment.

There were no consistent differences between treatment groups in anxiety symptoms (except for insomnia symptoms) after 8 weeks of treatment. The HAM-A score did, however, show greater improvement in the zolpidem tartrate extended-release/escitalopram treatment group at Week 1. This improvement was related to the early improvement in insomnia in the zolpidem tartrate extended-release/escitalopram treatment group, and was reflected only in the sleep-related item of the HAM-A.

The zolpidem tartrate extended-release/escitalopram treatment group had significantly greater improvement than the placebo/escitalopram treatment group on the following secondary sleep-related variables:

- Ratings of sleep quality
- Morning energy and morning concentration
- Impact of sleep on daily activities
- Number of awakenings
- Patient global impressions of treatment helpfulness to sleep, sleep latency, total sleep time, sleep quality, and medication strength

The zolpidem tartrate extended-release/escitalopram treatment group had greater improvement than the placebo/escitalopram treatment group in overall scores of clinical impressions of mental illness severity and global improvement of mental illness.

The zolpidem tartrate extended-release/escitalopram treatment group had significantly greater improvement than the placebo/escitalopram treatment group on several measures of daily functioning and quality of life, including the following:

- Energy/fatigue
- Wakefulness/alertness
- Satisfaction with sleep
- Emotional impact
- Daily activities

The zolpidem tartrate extended-release/escitalopram treatment group was comparable to the placebo/escitalopram treatment group on the following secondary efficacy variables: disability due to anxiety and insomnia; quality of life in relation to life enjoyment and satisfaction; quality of life in relation to cognitive functioning; and utilization of healthcare resources.

Safety results:

Type of event	Placebo plus escitalopram (N=190) n (%)	Zolpidem tartrate extended-release plus escitalopram (N=191) n (%)
Patients with any TEAE	134 (70.5)	146 (76.4)
Patients with serious TEAEs	1 (0.5)	1 (0.5)
Deaths	0 (0)	0 (0)
Patients with TEAEs leading to discontinuation of investigational product	13 (6.8)	13 (6.8)

Zolpidem tartrate extended-release/escitalopram treatment was well tolerated in this study. The nature, frequency, and intensity of TEAEs were within acceptable limits and were similar between treatment groups. The most frequently reported TEAEs (reported by =10% of patients in either treatment group) that occurred more often in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram treatment group were nausea, dizziness, and fatigue.

Laboratory values, vital signs, and physical examination findings revealed no meaningful changes or clinically relevant differences between the treatment groups.

Discontinuation of placebo and zolpidem tartrate extended-release resulted in no significant sleep loss relative to baseline TST.

Date of report: 28 August 2007