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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00296179
		Study Code:	PM_L_0166
Generic drug name:	Zolpidem Tartrate Extended Released	Date:	25/July/2008

Title of the study: A Comparison of Zolpidem Tartrate Extended-Release vs. Placebo in the Treatment of Insomnia Associated with Newly Diagnosed Major Depressive Disorder (MDD) or Untreated MDD Relapse, when used Concomitantly with Escitalopram (Study Number PM_L_0166)

Investigators: multicenter

Study centers: 41 centers in the USA

Publication (reference): none

Study period: Date first patient enrolled: 15-Feb-2006 Date last patient completed: 28-Jun-2007	Phase of development: IV (comparison)

Primary objective: To demonstrate overall improvement of insomnia (as measured by subjective Total Sleep Time) in patients with comorbid MDD who are treated with zolpidem tartrate extended-release and escitalopram vs. patients treated with placebo and escitalopram.

Secondary objectives: To show that treating insomnia from the beginning of SSRI treatment for depression results in improvement in other sleep parameters, improvement in quality of life measurements, and potentially greater response to antidepressant therapy at 8 weeks.

To test the hypothesis that improved sleep reduces the occurrence of relapse of depression by comparing the rates of relapse of MDD between placebo/escitalopram and zolpidem tartrate extended-release/escitalopram groups in patients who have responded to antidepressant therapy.

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

Methodology: This study was a randomized, double-blind, parallel-group, placebo-controlled trial of 12.5 mg zolpidem tartrate extended-release in adults with insomnia associated with MDD who were treated concomitantly with escitalopram. Patients received 8 weeks of treatment in Phase I. Patients whose depression responded to treatment were eligible to continue treatment with double-blind study medication in Phase II for an additional 16 weeks.

Number of patients:

Planned for Phase I: 260 completed patients required for analysis (377 planned to be randomized)

Randomized: 385

Treated: 382 received at least 1 dose of study medication

Continued to Phase II: 191

Evaluated:

Population	Phase I	Phase II
Efficacy		
ITT	380	187
Per-protocol	307	165
Safety	382	191

Diagnosis and criteria for inclusion: Adults who met the diagnostic requirements of MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and confirmed by the Mini International Neuropsychiatric Interview (MINI), and who also scored between 6 and 15 (inclusive) on the Quick Inventory of Depressive Symptomatology (QIDS-SR16) and experienced sleep disturbances at least 3 nights per week for at least 4 weeks prior to study entry. In addition, on at least 3 of the last 7 nights prior to randomization patients were to have had sleep disturbance (defined as Total Sleep Time [TST] <6.5 hours and/or sleep latency>30 minutes).

Investigational product: Zolpidem tartrate extended-release

Dose: 12.5 mg nightly

Administration: Oral

Duration of treatment: 8 weeks of randomized treatment in Phase I. Patients whose depression responded to treatment (≥50% reduction in HAM-D17 score) continued to Phase II and received an additional 16 weeks of double-blind treatment. All patients received an additional 2 weeks of treatment with open-label escitalopram after the end of the randomized treatment period.

Duration of observation: For patients in Phase I, observation was for 10 weeks after first dose of study medication. For patients continuing to Phase II, observation was for 26 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 reports of TST per night, measured by the Morning Sleep Questionnaire (MSQ) over the time period between visits at Week 6 and Week 8. Secondary measures included patient questionnaire responses about sleep characteristics (MSQ), depression symptoms (HAM-D17 and MDD symptoms), quality of life (SIS, QLES-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 at regular intervals. For most efficacy variables, statistical analyses were presented for the change in scores from baseline to each study visit.

Safety: AEs reported by the patient or noted by the investigator, standard hematology, chemistry, and 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 in Phase I 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. Data for Phase I and Phase II were analyzed separately.

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 patient. 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. Phase I and Phase II data were analyzed separately for AEs, vital signs, and sleep characteristics in the follow-up period.

Compliance and medication exposure were analyzed descriptively by treatment group. Treatment groups were compared using one-way ANOVA. Data for Phase I and Phase II were analyzed separately.

Summary:

Efficacy results:

Phase Variable	Placebo plus escitalopram	Zolpidem tartrate extended-release plus escitalopram	p-value for difference in improvement
Phase I (change from baseline value to week 8)	(N=190)	(N=190)	
Change in total sleep time (min)	64.00	101.4	<0.0001
Change in sleep onset latency (min)	-25.6	-45.0	<0.0001
Change in wake time after sleep onset (min)	-25.8	-45.2	0.0001
Change in Hamiltong Rating Scale for Depression (HAM-D17) total score	-10.8	-11.4	0.3003
Phase II (change from baseline value to week 24)	(N=94)	(N=95)	
Change in total sleep time (min)	93.89	114.2	0.1244
Change in sleep onset latency (min)	-42.5	-46.7	0.8106
Change in wake time after sleep onset (min)	-33.4	-43.1	0.1665
Change in HAM-D17 total score	-14.1	-14.6	0.3421
Depression relapse rate (%)	6.4%	3.2%	0.2845

The zolpidem tartrate extended-release/escitalopram treatment group had significantly greater improvement in TST (as measured by the MSQ) than patients treated with placebo/escitalopram; the difference between treatment groups was statistically significant at all visits during the 8 weeks of treatment in Phase I. This statistically significant treatment group difference was maintained in Phase II through Week 16 ($p<0.05$).

At all visits in Phase I the zolpidem tartrate extended-release/escitalopram group also had significantly greater improvement than the placebo/escitalopram treatment group on all other sleep characteristics measured by the MSQ (sleep onset latency, number of awakenings, wake time after sleep onset, sleep quality, morning energy, morning concentration, the impact of sleep on daily activities) at all visits. These treatment group differences were maintained throughout Phase II for several MSQ variables (number of awakenings, sleep quality, morning energy, and sleep impact on daily activities).

Patients in the zolpidem tartrate extended-release/escitalopram group also rated their insomnia treatment as superior to patients in the placebo/escitalopram group at all visits in both Phase I and Phase II on all PGI-IT variables: helpfulness to sleep, sleep latency, total sleep time, sleep quality, and medication strength.

Patients' depression improved in both treatment groups, but zolpidem tartrate extended-release/escitalopram did not significantly augment the antidepressant response to escitalopram. During Phase I, the zolpidem tartrate extended-release/escitalopram group achieved numerically greater improvement in HAM-D17 total score and numerically higher response and remission rates of depression than the placebo/escitalopram group. However, these differences were not statistically significant at any visit except for depression remission at Week 6.

In Phase II, HAM-D17 total score and depression remission continued to show greater numeric improvement in the zolpidem tartrate extended-release/escitalopram group compared with the placebo group, but never achieved statistical significance. Depression relapse was comparable in the two groups in Phase II. However, in all visits in both Phase I and Phase II, the total improvement in insomnia-only items of the HAM-D17 was significantly superior in the zolpidem tartrate extended-release/ escitalopram group compared to the placebo/escitalopram group.

The treatment groups had comparable improvement on scales measuring overall mental illness severity (CGI-Severity) and improvement (CGI-Improvement); there were no significant treatment group differences on these measures at any visit in Phase I or Phase II.

On most measures of daily functioning and quality of life, the zolpidem tartrate extended-release/escitalopram treatment group had greater improvement than the placebo/escitalopram treatment group in Phase I. Statistically significant treatment group differences were found for the following measures in Phase I, as assessed at Week 4 and Week 8:

- SIS domains of daily activities, emotional well-being, emotional impact, energy/fatigue, social well-being, mental fatigue (at Week 4 only), and satisfaction with sleep
- Q-LES-Q variables of physical health/activities (at Week 4 only) and household duties
- MGH-CPFQ variables of total score, motivation/interest/enthusiasm (Week 4 only), wakefulness/alertness, energy, focus/sustain attention (Week 4 only), remember/recall, and sharpness/mental acuity

Although the effects in Phase II were not as strong and consistent as in Phase I, the zolpidem tartrate extended-release/ escitalopram treatment group had greater improvement than the placebo/escitalopram treatment group in Phase II on the following measures as assessed at Weeks 12, 16, 20, and 24:

- SIS domains of emotional impact, energy/fatigue, social well-being, and satisfaction with sleep (Weeks 12, 16, 20, and 24), daily activities (Weeks 12, 20, and 24), and emotional well-being (Weeks 16, 20, and 24)
- Q-LES-Q variables of physical health/activities (Weeks 16, 20, and 24), work (Week 12), household duties (Weeks 16 and 20), and leisure time activities (Weeks 12 and 16)
- MGH-CPFQ variables of motivation/interest/enthusiasm (Week 16), wakefulness/alertness (Week 16), and energy (Weeks 12, 16, and 20)

The treatment groups were comparable in utilization of healthcare resources (as measured by the HRU) in both Phase I and Phase II.

Safety results :

Phase Type of event	Placebo plus escitalopram n(%)	Zolpidem tartrate extended-release plus escitalopram n(%)
Phase I	(N=190)	(N=190)
Patients with any treatment-emergent adverse event (TEAE)	126 (66.3)	140 (72.9)
Patients with any serious TEAE	01 (0.5)	2 (1)
Patients with TEAEs leading to discontinuation of investigational product	7 (3.7)	15 (7.8)
Deaths	0	0
Phase II	(N=95)	(N=96)
Patients with any TEAE	57 (60.0)	55 (57.3)
Patients with any serious TEAE	1 (1.1)	1 (1.0)
Patients with TEAEs leading to discontinuation of investigational product	1 (1.1)	1 (1.0)
Deaths	0	0

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 generally similar between treatment groups. In Phase I, a slightly greater percentage of patients had TEAEs in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram treatment group (72.9% vs. 66.3%). In Phase II the percentage of patients with TEAEs was similar in the zolpidem tartrate extended-release/escitalopram group and the placebo/escitalopram group (57.3% vs 60.0%).

In Phase I, the TEAEs that were reported by ≥5% of patients in either treatment group and occurred more often in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram treatment group were nausea (10.9% and 8.4%, respectively), somnolence (8.9% and 8.4%, respectively), dry mouth (6.8% and 5.3%, respectively), dizziness (6.3% and 2.1%, respectively), sedation (5.7% and 4.7%, respectively), fatigue (5.7% and 3.7%, respectively), upper respiratory tract infection (5.7% and 2.1%, respectively), and libido decreased (5.2% and 3.2%, respectively). Of note, in Phase I, some TEAEs reported less frequently (<5%) occurred in at least 3% more patients in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram treatment group: constipation (4.2% vs. 0%) and amnesia (3.6% vs. 0%).

In Phase II, the TEAEs that were most frequently reported (≥5%) and had a higher incidence in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram treatment group were headache (8.3% vs. 6.3%) and diarrhea (8.3% vs. 4.2%). Of TEAEs reported less frequently, 2 TEAEs occurred in at least 3% more patients in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram treatment group: blood pressure increased (4.2% vs. 1.1%) and blood pressure diastolic increased (3.1% vs. 0%).

Only 5 patients (2 in the placebo/escitalopram group and 3 in the zolpidem tartrate extended-release/escitalopram group) had treatment-emergent SAEs. None of the treatment-emergent SAEs in the zolpidem tartrate extended-release/escitalopram group were categorized by the Investigator as related to study medication.

In Phase I a greater percentage of patients in the zolpidem tartrate extended-release/escitalopram treatment group than in the placebo/escitalopram group had TEAEs leading to discontinuation (7.8% vs. 3.7%). Psychiatric disorders led to discontinuation in 6 patients in the zolpidem tartrate extended-release/escitalopram treatment group (vs. 1 patient in the placebo/escitalopram group). Two of these events (depression and suicidal ideation) were categorized by the investigator as unrelated to investigational product or escitalopram, and 4 of the events (anxiety, restlessness, hallucination, and hypnopompic hallucination) were categorized as possibly related to investigational product and/or escitalopram.

In Phase II, 1 patient in each treatment group discontinued investigational product because of TEAEs (nausea in the zolpidem tartrate extended-release/escitalopram group and suicide attempt in the placebo/escitalopram group). Laboratory values, vital signs, and physical examination findings revealed no clinically relevant differences between the treatment groups. Discontinuation of placebo and zolpidem tartrate extended-release resulted in no statistically significant sleep loss relative to baseline TST. Also, there was no statistically significant worsening from baseline in any other sleep characteristic measured by the MSQ. Conclusions: Overall, zolpidem tartrate extended-release was effective and well tolerated as treatment for insomnia in patients who had comorbid MDD. Zolpidem tartrate extended-release also improved many aspects of quality of life and daily functioning, and some of these effects lasted the entire length of treatment (up to 24 weeks). Major depression symptoms improved in both the zolpidem tartrate extended-release/escitalopram and placebo/escitalopram groups. However, the addition of zolpidem tartrate extended-release did not appear to significantly augment the effects of escitalopram on depression.
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