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Prescribing decisions should be made based on the approved package insert in the country of prescription.

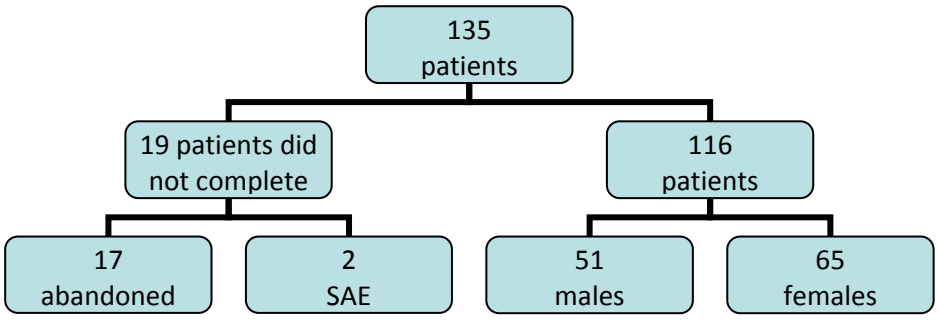
Sponsor / Company : sanofi-aventis **Drug Substance** : ZOLPIDEM			**Study Identifier** :NCT01024192 **Study Code** : ZOLPI_L_04134
Title of the study	Efficacy and safety assessment of **ZO**lpidem (Stilnox® CR) administered on "as needed" basis in patients with chronic insom**NIA**		
Study centers	13 centers		
Study period	Date first patient enrolled: 06-Nov-2009 Date last patient completed: 29-Jul-2010		
Phase of development	Phase IV		
Objectives	Primary objective: To evaluate the efficacy and safety of the use of Stilnox CR on an "as needed" basis in Mexican patients with chronic insomnia at the prescription conditions of daily practice. Secondary objective: To evaluate the satisfaction of the patient with chronic insomnia with Stilnox CR over an "as needed" basis.		
Methodology	Multicenter, open, phase IV study during a 12 week period (3 months) for every participating subject.		
Number of patients/subjects	Planned: 130	Randomized: Not applicable	Treated: 135
Evaluated	Efficacy: 116	Safety: 135	
Diagnosis and criteria for inclusion	• Men and Women • 18 to 65 years of age • Primary insomnia diagnosis (difficulty for initiating sleep, or maintaining sleep; to wake up to early in the morning, or to present a restless sleep) which causes clinically significant disturbances in the areas of social, work functioning or other important areas • Informed consent • To be able to accomplish the study requirements		
Investigational product Dose: Administration:	Stilnox® CR 12.5 mg oral		
Duration of treatment	3 months follow-up from the first visit		
Duration of observation	3 months follow-up from the first visit		

Criteria for evaluation Efficacy:	The primary efficacy variable was assessed on the Intent to Treat population (ITT), defined as the population who receives at least one dose of the study medication and has at least one primary endpoint assessment at inclusion and after baseline. • The primary efficacy criterion was the improvement on the Clinical Global Impression [CGI] from baseline to the end of the study, measured by a qualitative questionnaire. • The secondary efficacy population was the Per Protocol population (PP), defined as all patients who adhered to protocol: 1. As per the Clinical Global Impression [CGI] o Improvement of Illness severity from baseline to the end of study o Efficacy rate determined by a therapeutic effect-side effects evaluation questionnaire 2. Patients satisfaction questionnaire scores
Safety:	Safety evaluation was assessed in the Intent To Treat population, solicited and reported in the corresponding Case Report Form (CRF).
Statistical methods	Sample size: 112 plus 15% of drop-out patients during the study equals a total of 130 pts. Distribution: 10 patients per center Statistical power and sample size justification: The sample size estimation was performed based on the response variable (proportion of patients that after 15 days of treatment showed improvement, defined as those experiencing fewer difficulties to sleep: insomnia symptoms reduction). Based on the article "Extended-release zolpidem: efficacy and tolerability profile", Drugs of today 2006, 42 (11): 721-727 by Owen R.T. which reported 82.3% improvement in patients in maintaining sleep after a 15 day treatment, yielding next scenarios: Initially, the type-I error was established at 5% (α=0.05), and the type II error at 20% (β=0.20), in order to present the different scenarios for the variations to achieve an efficacy percentage in terms of responders with a confidence interval of 95% and a statistical power of 80%. The most recommended scenario for efficacy was established with a minimum number of 112 valid patients; which means 130 patients to be recruited; a 15% drop-out, to achieve a 5% amplitude interval, considering a confidence interval of 95% and a power of 80%. Statistical Methods: Both parametric and non parametric variables were analyzed observing the planned confidence interval of 95% Mode, median, average standard deviations and ranges are provided in the description of data series. Paired t test and ANOVA analysis were performed to compare paired groups of data.

Summary

Efficacy:

A total of 135 patients were included; 20 did not complete the study: 17 abandoned the study; 2 due to adverse effects, and one reported lack of efficacy. Nevertheless all were included in the safety and efficacy analysis. Overall, 115 patients completed the 3 month intervention study.

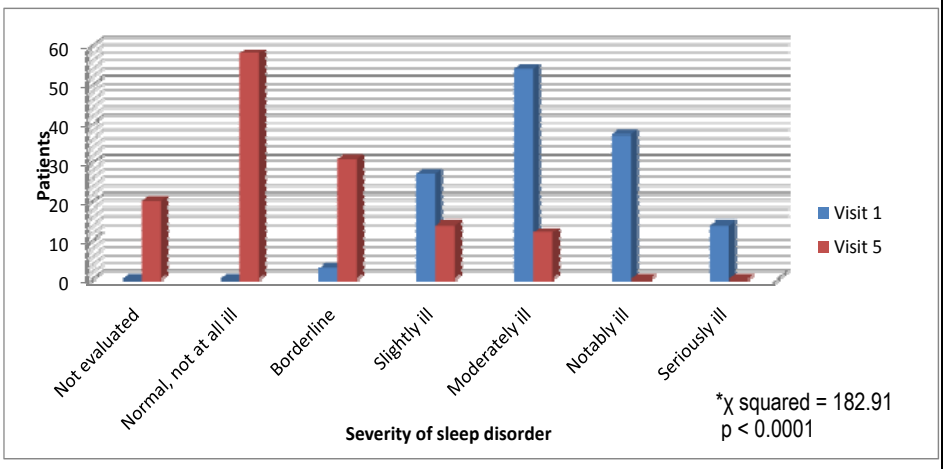


Demographic variables	Mean	Standard deviation
Age [years]	44.9	13.8
Weight [kg]	70.6	13.0
Height [cm]	164.7	10.3
BMI [kg/m²]	26	3.6

Gender distribution: 75 females (56%); 60 males (44%).

Three different parameters were considered to assess efficacy and safety: a) severity of sleep disorder; b) Global improvement ; c) Therapeutic effect - side effects relation

a) Results about severity of sleep disorder from baseline to the end of study



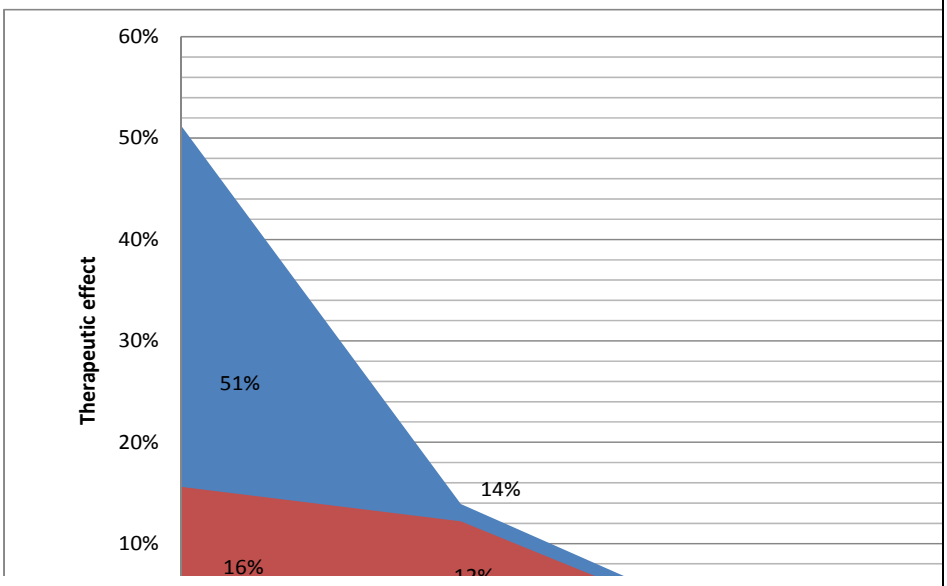
The proportion of patients considered as “Normal, not at all ill” increased significantly at visit 5. As of proportion of patients under “moderately”, “notably” and “seriously ill” groups significantly decreased by the end of study.

b) Results of global improvement of patients survey:

Global Improvement	%	Frequency
Not evaluated	14.1%	19
Much improved	52.6%	71
Improved	31.1%	42
Minimally improved	1.5%	2
No change	0.7%	1
Minimally worsened	0%	0
Worse	0%	0
Much worse	0%	0
Total	**100%**	**135**

After visit 5, 83.7% of patients were considered as "improved" or "much improved". No patient was considered as worsened. Drop-out patients were considered in the "not evaluated" category.

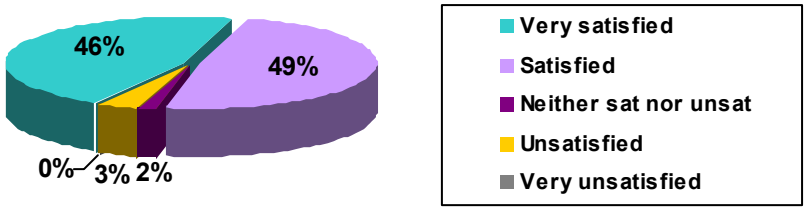
c) Results of evaluation of therapeutic effect - side effect:

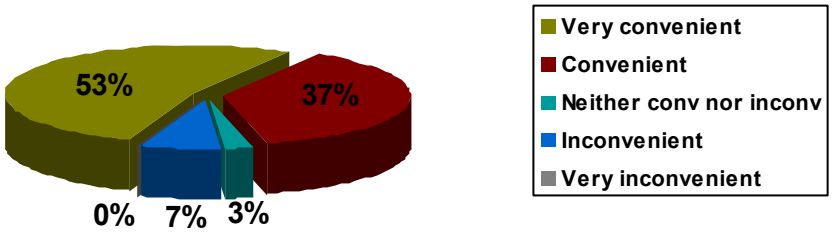
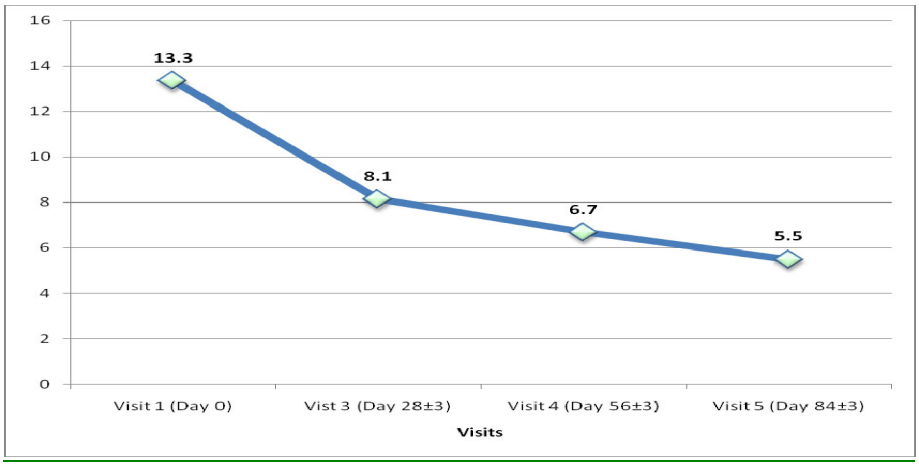


51.3% of the patients obtained a prolonged therapeutic effect with no side effects. Just a 3.5% of the patients had some level of therapeutic effect with significantly and very important side effects

The evaluation of patient satisfaction with the treatment and therapeutic scheme was made by patients using a self-administered questionnaire. Results are shown in the following figures:

Patient's satisfaction with treatment



	Patient's opinion regarding the "use as needed" therapeutic scheme  Finally, in the analysis of the Pittsburgh Sleep Quality Index (PSQI), the average values of the global scores showed an improvement with a decrease of 7.8 points from baseline visit (13.3 pts) to visit 5 (5.5 pts) with a significant difference (F = 114.06, g.l. = 3, p < 0.01).  An additional analysis of tablets consumed between visits was performed using a weighting factor balance in the period of time between visits and the number of patients throughout the study due to the existence of variations in both criteria. An average of 0.5 tablets per day was obtained, representing a consumption of one tablet every other day.
Safety results:	Adverse events were collected in the CRF and evaluated in the initial 135 patients included in the study. Overall, 53 different adverse events were reported, occurring 144 times in 47 patients, which represents an average of 1.13 adverse events per patients. Only one serious adverse event was reported and not related to the study drug (right clavicle fracture). Two patients dropped-out the study due to adverse events that were not considered Serious Adverse Events (SAEs), such as headache, nausea, hyporexia, dry mouth, excessive worries, anxiety and rebound insomnia. In the study population, the most common adverse effect was headache (25.7%), followed by excessive somnolence (5.6%), anxiety (4.9%) and nausea (4.2%). Proportion of patients reporting adverse events versus those with no adverse events was compared for each visit and a significant difference was observed in the statistical tests in the latest.
Issue date:	23 April 2012